CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-856

MEDICAL REVIEW(S)

Addendum: Study Design and Conduct

I. Introduction

A brief description of the design and conduct of Study F-GT06-153 is given in the body of the Clinical Review. This addendum will provide additional details. All references are to the Phase 3 trial designated F-GT06-153 (Study F-153).

II. Study Rationale

Previous studies established the efficacy of febuxostat 80 mg and 120 mg daily in lowering urate levels in patients with hyperuricemia and gout. These included both placebo and allopurinol controlled studies. No Phase 3 trial assessing the efficacy and safety of lower doses of febuxostat in the U.S. had been undertaken prior to initiation of the current trial. Febuxostat 40 mg daily had been studied in a 4 week Phase 2 trial with a placebo control; 56% of subjects taking the lower dose of febuxostat achieved a sUA < 6 mg/dL and the difference between this and placebo was statistically significant. This new trial (Study F-153) was designed to evaluate the efficacy and safety of febuxostat 40 mg and 80 mg daily compared to allopurinol for lowering serum urate in subjects with hyperuricemia and gout.

Since patients with gout often have concomitant renal impairment, subjects with renal impairment were intended to be included in this study.

III. Study Objective

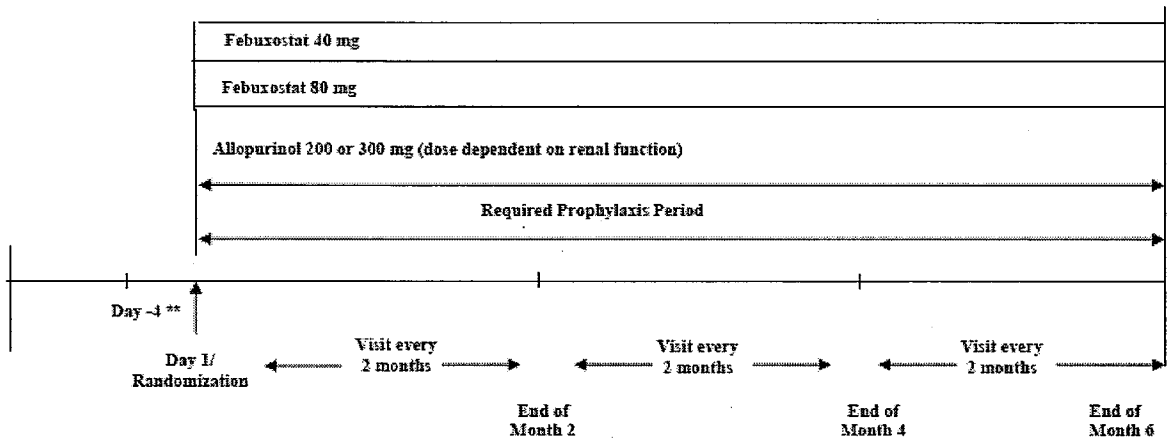
The objective of this study was to compare the efficacy and safety of febuxostat 40 mg QD and febuxostat 80 mg QD doses to allopurinol in subjects with hyperuricemia and gout.

IV. Study Design

This trial was planned as a Phase 3, randomized, double-blind, multicenter, active-controlled study. Screening was planned at approximately 300 US sites with a target enrollment of approximately 2,250 subjects who would be randomized 1:1:1 to: febuxostat 40 mg QD, febuxostat 80 mg QD or allopurinol. Randomization was to include stratification by baseline renal function. Treatment duration of 6 months was planned. The dose of allopurinol was to be determined by baseline renal function: patients with normal renal function (creatinine clearance $\geq$ 80 mL/min) would be given

allopurinol 300 mg QD while those with renal impairment (creatinine clearance: 20-79 mL/min) would be given allopurinol 200 mg QD.[1] Figure 1 provides an overview of the study design.

Figure 1. F-GT06-153 Study Design



* Day -30 Screening Visit is required for subjects currently on ULTs. These subjects will start to receive TAP provided prophylaxis medications on the Day - 30 Screening Visit.

** Day -4 Visit is required for all subjects. It will serve as the Screening Visit for subjects currently not on ULTs.

Source: Clinical Study Report

A. Inclusion Criteria

The study was to include subjects with gout as defined by history and serum uric acid exceeding 8.0 mg/dL. In addition it was expected that 35% of the subjects would have impaired renal function. The objective of including a large number of subjects with renal impairment was operationalized by prespecifying that sponsor could terminate the enrollment of subjects with normal renal function in order to insure that this expectation would be met. The following inclusion criteria (paraphrased and abbreviated but taken directly from the Protocol) were specified:

1. Subjects need to sign appropriate informed consent forms and HIPAA authorizations (where needed). An IRB needed to have approved the informed consent form.

2. Subjects would be male or female between the ages of 18 to 85 years.

[1] Creatinine clearance was calculated by the Cockcroft-Gault formula corrected for ideal body weight.

3. Subjects would have a history or presence of gout, defined as having one or more of the American Rheumatism Association criteria for the diagnosis:

- A tophus proven to contain urate crystals
- Urate crystals in joint fluid and/or
- History of at least 6 of the following:
  - More than one attack of acute arthritis
  - Maximum inflammation developed within 1 day
  - Monarticular arthritis
  - Redness observed over joints
  - First metarsophalangeal joint painful or swollen
  - Unilateral first metatarsophalangeal joint attack
  - Unilateral tarsal joint attack\
  - Tophus (proven or suspected)
  - Hyperuricemia
  - Asymmetric swelling within a joint on x-ray
  - Subcortical cysts without erosions on x-ray
  - Joint fluid culture negative for organisms during attack
- Females must be:
  - Postmenopausal (amenorrhea for at least 2 years and age $\geq$ 50 years), or
  - Surgically sterile, or
  - Using a medically accepted means of contraception from 90 days priot to the start of the study until 30 days after the last dose. This included oral or injectable hormones or IUDS or a double barrier method.
- Subjects must have a sUA $\geq$ 8.0 mg/dL at the Day -4 visit.

B. Exclusion Criteria

In general patients with secondary hyperuricemia, severe renal impairment, severe liver disease, and/or other serious medical conditions were excluded. The following list is taken from the Protocol:

1. Subject is breast feeding or pregnant;
2. Subject has secondary hyperuricemia (eg, due to myeloproliferative disorder);
3. Subject has a history of xanthinuria;
4. Subject has received urate-lowering therapy (ie, allopurinol, probenecid, etc.) within 30 days prior to Day 1/Randomization Visit;
5. Subject has a known hypersensitivity to febuxostat or allopurinol or any components of their formulation; subject has a known hypersensitivity to naproxen, any other NSAID, aspirin, lansoprazole, colchicine, or any components in their formulation;
6. Subject has active peptic ulcer disease;
7. Subject has a history of cancer (other than basal cell carcinoma of the skin) within 5 years prior to the Screening Visit;
8. Subject has alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values >1.5 x the upper limit of normal;
9. Subject has rheumatoid arthritis which requires treatment;
10. Subject has a significant medical condition and/or conditions that would interfere with the treatment, safety or compliance with the protocol;
11. Subject has experienced either a myocardial infarction or stroke and is clinically unstable;
12. Subject consumes >14 alcoholic beverages/week. Subject has a history of alcoholism or illicit drug abuse within 5 years;
13. Subject has participated in another investigational study within the 30 days prior to the Screening Visit;
14. Subject's estimated creatinine clearance is <30 mL/min, where creatinine clearance is calculated using the Cockcroft-Gault formula corrected for Ideal Body Weight (IBW), as provided below:

C. Efficacy Endpoints

The primary endpoint was to be the proportion of subjects with sUA < 6.0 mg/dL at the final visit. A subject's final visit was defined as the latest visit with a serum urate level.

Secondary endpoints included: the proportion of subjects with renal impairment who achieved a sUA < 6 mg/dL; the proportion of subjects with sUA levels < 4, 5 and 6 mg/dL; and, the percent reduction from baseline in urate levels at each visit.

D. Safety Endpoints and Adverse Events

Well defined APTC endpoints (as described in the body of the Clinical Review) were used to assess cardiovascular adverse events. Other routine safety assessments (adverse events, physical exam findings, ECGs, and so on) will be collected at the scheduled visits as shown in Figure 2.

An adverse event (AE) was defined as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product...." It need not be causally related. Laboratory abnormalities, ECG and vital sign changes were to be considered to be AEs only if they resulted in discontinuation from the study.

Serious AEs (SAEs) were to include adverse experiences that resulted in death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of an existing hospitalization, a persistent/significant disability, or a congenital anomaly or birth defect. Criteria for each of these outcomes were specified.

AEs were classified as:

Mild: if transient and easily tolerated
Moderate: if it caused discomfort and interrupted a subject's usual activities
Severe: if it caused considerable interference with a subject's usual activities and may be incapacitating or life threatening.

Data on AEs was collected from the time the ICF was signed until 30 days following discontinuation of the study drug. Sponsor was to be notified by telephone within 24 hours of all SAEs or potential SAEs.

Electronic case report forms were to be used to transmit the data collected in this study to the Sponsor.

E. Concomitant Therapy

Use of prior, alternative urate lowering therapy (ULT) was not excluded. However, such therapy needed to be discontinued 30 days prior to randomization and was excluded for the duration of the study.

The following medications needed to be discontinued 4 days prior to the start of the study and were not permitted during the study: salicylates (except chronic use of ASA $\leq$ 325 mg/day), thiazide diuretics, losartan, azathioprine, mercaptopurine, theophylline, IV colchicine, cyclosporine, cyclophosphamide, pyrazinamide, sufamethoxazole/ trimethoprim, and use of corticosteroids (chronic prednisone $\leq$ 10 mg/day and short term use of higher doses of prednisone for gout flares was to be allowed). No changes in hormone replacement or oral contraceptive therapy was permitted within three months of the start of the study. No use of COX-2 or NSAIDS other than Sponsor-supplied naproxen was allowed.

F. Gout Flares

The main prophylactic agent was colchicine which was administered at a dose of 0.6 mg daily to prevent gout flares. If colchicine was not tolerated by the subject and if the subject had adequate renal function (creatinine clearance $\geq$ 50 mg/dL), then naproxen (250 mg BID) was to be given with concomitant lansoprazole.

For gout flares, subjects were able to increase colchicine to 0.6 mg BID or to take three additional doses of naproxen.

G. Treatment and Blinding

After enrollment and randomization to one of the three arms (Febuxostat 40 mg, Febuxostat 80 mg, or Allopurinol), subjects were to be given bottles containing 70 study drug capsules. They were to be instructed to take one capsule each morning; at subsequent study visits they were to be instructed to return the bottle at which time they would be given a new one.

In order to make the treatments indistinguishable, all three treatments used over-encapsulated iron gray opaque capsules. The sponsor, investigator, study coordinator and subject were to remain blinded throughout. The randomization schedule was to be computer–generated by Sponsor's statistics department.

Prophylactic medications were to be supplied by Sponsor. These were to remain unblinded.

H. Study Visits

The schedule of study visits and planned activities is depicted in Figure 2.

Study visits were scheduled at 30 days and 4 days prior to Day 1 (which was the randomization visit). Subsequent visits at the end of 2, 4 and 6 months were also scheduled. Figure 2 provides the schedule for examination, laboratory tests and other data collection.

All laboratory samples (except urine pregnancy) described in the protocol were to be sent to a central laboratory for analysis.

Figure 2. Study Schedule of Activities

PROCEDURE	Day -30* Screening Visit	Day -4** Visit	Day 1/ Randomization Visit	End of Month 2 Visit	End of Month 4 Visit	End of Month 6 Visit [c]
Informed consent/HIPAA Authorization (if required)	X	X[a]				
Medical History (including cardiovascular, gout and social history and medications)	X	X[a]				
Complete physical exam	X	X[a]				X
Presence of Tophi	X	X[b]				
Brief physical exam		X[a]	X	X	X	
12-Lead ECG	X	X[b]	X	X	X	X
Laboratory Tests [d]	X	X[g]		X	X	X
Serum pregnancy test[e]		X				X
Urine pregnancy test[e]	X					
Weight	X	X[a]				X
Height	X	X[a]				
Vitals (heart rate and blood pressure)	X	X	X	X	X	X
Dispense gout flare prophylaxis meds	X[a]		X	X	X	
Dispense double-blind study meds			X	X	X	
Gout flare assessment	X[f]	X[f]	X	X	X	X
Rash Assessment	X[f]	X[f]	X	X	X	X
AE Assessment	X[f]	X[f]	X	X	X	X
Concomitant Medication	X	X	X	X	X	X
Collection of unused double blind study drugs				X	X	X
Collection of unused gout flare prophylaxis (study drug compliance)			X[a]	X	X	X
IVRS (For subject study number, confirmation of prophylaxis meds and/or study drug assignment)	X	X[a]	X	X	X	

* Day -30 Screening Visit is for subjects currently on ULTs.

** Day -4 Visit is required for all subjects. Will serve as Screening Visit for subject not on prior ULTs. Subjects not on prior ULTs must also complete all procedures from Day -30 Screening Visit with the exception of the urine pregnancy test.

a Required only for subjects on ULTs at Day -30 Screening Visit.

b Required only for subjects not on prior ULTs.

c Or upon premature termination.

d Complete Chemistry Panel, sUA level, Hematology and Urinalysis; Coagulation PT and aPTT should be collected for all subjects. INR levels will be assessed for subjects on warfarin.

e All female subjects of childbearing potential.

f Site will start to document assessment of gout flare(s), adverse events, and presence of rash(es).

g The Day -4 labs may be retested once, however, retesting must occur within 7 days of initial screening. The repeat testing will include the chemistry and hematology panels, and a urinalysis.

Source. Clinical Study Report

I. Statistics

Analysis of efficacy was to be based on the intention-to-treat population which was defined as all randomized subjects who take at least one dose of study drug and who had sUA $\geq$ 8 mg/dL at the Day -4 visit. All randomized subjects who had received one dose of study drug were to be included in the safety analysis.

The primary efficacy comparison was between febuxostat 40 mg daily and allopurinol. In undertaking this comparison, two steps were anticipated. First, an evaluation to establish non-inferiority to allopurinol would be completed. In order to accomplish this evaluation, binomial 95% confidence intervals were to be calculated; non-inferiority would be established if the lower bound of the 95% confidence interval for the difference between febuxostat and allopurinol is greater than (-10%). If febuxostat 40 mg were confirmed as non-inferior to allopurinol, then a second evaluation for superiority would

be performed. This second step would use Fisher's exact test with a two-tailed 0.05 significance level.

For secondary efficacy variables, it is important to note that no adjustments for multiple comparisons were planned.

Safety was to be evaluated by consideration of the incidence of adverse events including cardiovascular AEs. A more complete description of the evaluation of cardiovascular AEs and APTC endpoints can be found in the body of the Clinical Review.

The sample size (2250 subjects) was chosen to provide: at least 90% power to meet the non-inferiority criteria between febuxostat 40 mg and allopurinol, and, at least 90% power to detect a 10% difference between febuxostat 40 mg and allopurinol for the primary efficacy variable, and, also, at least 90% power to detect a 10% difference for the comparison of febuxostat 40 mg with febuxostat 80 mg.

J. Study Design - Conclusions

The study design, overall, was compatible with the objectives of assessing the safety and efficacy of febuxostat 40 mg and 80 mg doses. The duration of six months was adequate to establish efficacy and demonstrate that sUA decreased to the prespecified level. As described in the Clinical Review, a major purpose of Study F-153 was to assess whether cardiovascular events noted in earlier trials would be replicated, and the duration of six months was adequate for this purpose. The duration of the trial was not long enough to exclude toxicity that could result from long-term exposure to febuxostat. However, this was not the intent of this study; two long term open-label trials (one lasting for five years) had been completed previously.

Inclusion criteria appeared adequate to capture the target population of patients with hyperuricemia and gout. Exclusion criteria also appeared to be appropriate.

Efficacy and safety endpoints were well defined with reasonable procedures designed to measure these.

Prophylaxis against gout flares with either colchicine or naproxen for the entire duration of the trial (6 months) may have been excessive and did eliminate the ability to characterize the rate of flares once prophylaxis is discontinued. Since data describing the flare rate after discontinuation of prophylaxis had been accumulated in previous trials, the primary bias that could have been introduced by the use of prophylaxis for six months was likely to have been to reduce the total number of AEs by reducing the total number of gout flares. Since, however, subjects with the active comparator, allopurinol, also received prophylaxis for six months, it does not appear that a bias would have been introduced into the comparison between febuxostat and allopurinol.

The use of over-encapsulated tablets is a common blinding technique that would appear to adequately preserve blinding. Since there are no specific side effects that are both common and also unique to one or the other of the study drug there do not appear to be other factors that could lead to unblinding.

The choice of an ITT population for the primary analysis is inclusive and appropriate. The choice of a final visit serum urate measurement preserves the number of subjects that can be analyzed. It is not conducive to exclusion of dropouts due to failure of treatment. Choice of a 10% inferiority margin for comparison of febuxostat 40 mg and allopurinol would preserve 75% of the treatment effect of allopurinol. (The treatment effect of allopurinol has been shown previously to be at approximately 40%.)

V. Study Conduct

A. Enrollment by Center

The study was carried out at 324 US sites. Most of these had enrollment of fewer than 10 subjects; 75 sites enrolled 10 or more subjects. The largest number of subjects enrolled at one site was 69.

The large number of study sites would minimize the chance that the misconduct of any one or two sites would influence the overall results, though it does not exclude this possibility. Rather, the largest problem that could result from use of a large number of sites with only a small number of subjects in each one, would be inconsistency of interpretation of guidelines. Since, however, it is reasonable to assume that inconsistency would not always result in the same error of interpretation, this is unlikely to introduce a systematic bias into study results. It might, however, introduce a lack of precision into results which could be spread over a large number of possible outcomes.

B. Subject Disposition

The disposition of subjects is displayed in Table A-1. Perusal of the bottom half of the table reveals that there is a statistically significant difference between the percent of premature discontinuations in the febuxostat 80 mg arm compared with febuxostat 40 mg (21 % vs. 17%). This difference holds for all but one of the six time periods identified.

The reasons for premature discontinuation are given in Table A-2. One notes here that discontinuation for AEs (as a primary reason) was highest in subjects receiving allopurinol (9%) and was closely followed by subjects receiving febuxostat 80 mg (8%). Somewhat fewer subjects receiving febuxostat 40 mg discontinued for AEs (7%). The table further demonstrates that compared with subjects in the other two arms, those in the febuxostat 80 mg arm were more likely to discontinue for personal reasons, withdrawal of consent, gout flare and "lost to follow-up." Overall, no specific pattern emerges to

suggest that febuxostat was associated with a specific problem leading to premature discontinuation.

Table A-1. Subject Disposition

Evaluation	Febuxostat 40 mg QD (N= 757)	Febuxostat 80 mg QD (N= 756)	Allopurinol 300/200 mg QD (N= 756)&	All Subjects (N= 2269)
Number of Subjects Randomized and Received At Least One Dose of Study Drug	757	756	756	2269
Number of Subjects Included in ITT Population #	757 (100.0%)	756 (100.0%)	755 (99.9%)	2268 (100.0%)
Reason for Exclusion from the ITT Population				
Serum Urate < 8.0 mg/dL at Day -4 Visit			1 (0.1%)	1 (0.0%)
Number of Subjects Prematurely Discontinued	125 (16.5%)	158 (20.9%)	135 (17.9%)	418 (18.4%)
Timing of Premature Discontinuation (days)				
1 to 30 [Month 1]	34 (4.5%)	48 (6.3%)	38 (5.0%)	120 (5.3%)
31 to 60 [Month 2]	16 (2.1%)	19 (2.5%)	28 (3.7%)	63 (2.8%)
61 to 90 [Month 3]	27 (3.6%)	37 (4.9%)	27 (3.6%)	91 (4.0%)
91 to 120 [Month 4]	15 (2.0%)	17 (2.2%)	10 (1.3%)	42 (1.9%)
121 to 150 [Month 5]	22 (2.9%)	20 (2.6%)	22 (2.9%)	64 (2.8%)
>= 151 [Month 6]	11 (1.5%)	17 (2.2%)	10 (1.3%)	38 (1.7%)

& Distributed as: allopurinol 200 mg (N=145) plus allopurinol 300 mg (N=611).
# The intent-to-treat population (ITT) is defined as all randomized subjects who received at least one dose of study drug and who had serum urate level >=8.0 mg/dL at the Day -4 Visit.

Evaluation	P-value @ FEB 40 vs ALLO	FEB 80 vs ALLO	FEB 40 vs FEB 80
Number of Subjects Randomized and Received At Least One Dose of Study Drug			
Number of Subjects Included in ITT Population #			
Reason for Exclusion from the ITT Population			
Serum Urate < 8.0 mg/dL at Day -4 Visit			
Number of Subjects Prematurely Discontinued	0.496	0.152	0.030*
Timing of Premature Discontinuation (days)			
1 to 30 [Month 1]			
31 to 60 [Month 2]			
61 to 90 [Month 3]			
91 to 120 [Month 4]			
121 to 150 [Month 5]			
>= 151 [Month 6]			

& Distributed as: allopurinol 200 mg (N=145) plus allopurinol 300 mg (N=611).
# The intent-to-treat population (ITT) is defined as all randomized subjects who received at least one dose of study drug and who had serum urate level >=8.0 mg/dL at the Day -4 Visit.
Note: FEB 40 - Febuxostat 40 mg QD, FEB 80 - Febuxostat 80 mg QD, ALLO - Allopurinol 300/200 mg QD.
@ P-values for pairwise comparisons are from Fisher's exact test.
*, **, *** indicates statistical significance at the 0.05, 0.01, or 0.001 level, respectively.

Table A-2. Primary and Secondary Reasons for Premature Discontinuation

Evaluation	Febuxostat 40 mg QD (N= 757)	Febuxostat 80 mg QD (N= 756)	Allopurinol 300/200 mg QD (N= 756)&	All Subjects (N= 2269)
Number of Subjects Prematurely Discontinued	125 (16.5%)	158 (20.9%)	135 (17.9%)	419 (18.4%)
Primary Reason for Premature Discontinuation				
Adverse Events	49 (6.5%)	61 (8.1%)	64 (8.5%)	174 (7.7%)
Protocol Violation	10 (1.3%)	2 (0.3%)	4 (0.5%)	16 (0.7%)
Personal reasons(s)	12 (1.6%)	24 (3.2%)	9 (1.2%)	45 (2.0%)
Lost to Follow-Up	28 (3.7%)	33 (4.4%)	28 (3.7%)	89 (3.9%)
Therapeutic Failure	1 (0.1%)	1 (0.1%)	1 (0.1%)	3 (0.1%)
Withdrew Consent	14 (1.9%)	20 (2.6%)	16 (2.1%)	50 (2.2%)
Did not Meet Inclusion/Exclusion Criteria	0	2 (0.3%)	0	2 (0.1%)
Gout Flare	3 (0.4%)	7 (0.9%)	2 (0.3%)	12 (0.5%)
Other	8 (1.1%)	8 (1.1%)	11 (1.5%)	27 (1.2%)
All Secondary Reasons for Premature Discontinuation +				
Protocol Violation	1 (0.1%)	1 (0.1%)	0	2 (0.1%)
Personal reasons(s)	4 (0.5%)	4 (0.5%)	5 (0.7%)	13 (0.6%)
Lost to Follow-Up	3 (0.4%)	1 (0.1%)	1 (0.1%)	5 (0.2%)
Therapeutic Failure	2 (0.3%)	1 (0.1%)	0	3 (0.1%)
Withdrew Consent	23 (3.0%)	26 (3.4%)	17 (2.2%)	66 (2.9%)
Gout Flare	4 (0.5%)	4 (0.5%)	0	8 (0.4%)
Other	3 (0.4%)	4 (0.5%)	4 (0.5%)	11 (0.5%)

& Distributed as: allopurinol 200 mg (N=145) plus allopurinol 300 mg (N=611)
+ Not all subjects had secondary reasons, and some subjects may have had more than one secondary reasons.

C. Baseline Demographics

Table A-3 displays the demographic characteristics of all subjects. The composition of the three arms of the study appears similar. Table 10 of the Clinical Review provides additional data on medical history and, as we concluded there, there does not appear to be an imbalance in the three arms of those with gout, cardiovascular disease, or other relevant medical history.

Table A-3: Demographic and Baseline Characteristics of All Subjects

Variable	Febuxostat 40 mg QD (N=757)	Febuxostat 80 mg QD (N=756)	Allopurinol 300/200 mg QD (N=756) &	All Subjects (N=2269)
Gender				
Male	722 (95.4%)	710 (93.9%)	709 (93.8%)	2141 (94.4%)
Female	35 (4.6%)	46 (6.1%)	47 (6.2%)	128 (5.6%)
Race				
American Indian or Alaska Native	6 (0.8%)	10 (1.3%)	6 (0.8%)	22 (1.0%)
Asian	26 (3.4%)	25 (3.3%)	37 (4.9%)	88 (3.9%)
Black or African American	83 (11.0%)	78 (10.3%)	67 (8.9%)	228 (10.0%)
Native Hawaiian or Other Pacific Islander	11 (1.5%)	10 (1.3%)	11 (1.5%)	32 (1.4%)
White	620 (81.9%)	618 (81.7%)	625 (82.7%)	1863 (82.1%)
Other	11 (1.5%)	15 (2.0%)	8 (1.1%)	34 (1.5%)
Missing	0	0	2 (0.3%)	2 (0.1%)
Ethnicity				
Hispanic or Latino	47 (6.2%)	49 (6.5%)	53 (7.0%)	149 (6.6%)
Not Hispanic or Latino	710 (93.8%)	707 (93.5%)	702 (92.9%)	2119 (93.4%)
Missing	0	0	1 (0.1%)	1 (0.0%)
Age (yr) #				
<45	192 (25.4%)	196 (25.9%)	180 (23.8%)	568 (25.0%)
45-<65	450 (59.4%)	432 (57.1%)	445 (58.9%)	1327 (58.5%)
>=65	115 (15.2%)	128 (16.9%)	131 (17.3%)	374 (16.5%)
N	757	756	756	2269
Mean	52.5	53.0	52.9	52.8
SD	11.68	11.79	11.73	11.73
Median	52.0	53.0	53.0	53.0
Min-Max	21-85	21-85	19-85	19-85

& Distributed as: allopurinol 200 mg (N=145) plus allopurinol 300 mg (N=611).
@ For categorical variables, p-value is from a Chi-square test.
For continuous variables, p-value is from a one-way analysis of variance using treatment as the factor.
At baseline.

Variable	Febuxostat 40 mg QD (N=757)	Febuxostat 80 mg QD (N=756)	Allopurinol 300/200 mg QD (N=756) &	All Subjects (N=2269)
Alcohol Use				
Non-/Ex-Drinker	242 (32.0%)	243 (32.1%)	235 (31.1%)	720 (31.7%)
Drinker	515 (68.0%)	513 (67.9%)	521 (68.9%)	1549 (68.3%)
Tobacco Use				
Non-/Ex-Tobacco User	625 (82.6%)	611 (80.8%)	623 (82.4%)	1859 (81.9%)
Tobacco User	132 (17.4%)	145 (19.2%)	133 (17.6%)	410 (18.1%)
Menopausal History (Females Only)				
Premenopausal	4 (0.5%)	3 (0.4%)	2 (0.3%)	9 (0.4%)
Perimenopausal	1 (0.1%)	1 (0.1%)	1 (0.1%)	3 (0.1%)
Postmenopausal	29 (3.8%)	42 (5.6%)	44 (5.8%)	115 (5.1%)
Missing	1 (0.1%)	0	0	1 (0.0%)

& Distributed as: allopurinol 200 mg (N=145) plus allopurinol 300 mg (N=611).
@ For categorical variables, p-value is from a Chi-square test.
For continuous variables, p-value is from a one-way analysis of variance using treatment as the factor.

Table A-3, continued

Variable	Febuxostat 40 mg QD (N=757)	Febuxostat 80 mg QD (N=756)	Allopurinol 300/200 mg QD (N=756) &	All Subjects (N=2269)
Weight (lb) #				
N	755	755	755	2265
Mean	229.8	227.3	225.5	227.6
SD	49.58	47.70	46.09	47.48
Median	225.0	222.0	220.0	222.0
Min-Max	117-449	102-474	102-425	102-474
Height (in) #				
N	757	756	755	2269
Mean	70.0	69.7	69.6	69.8
SD	3.29	3.31	3.32	3.31
Median	70.0	70.0	70.0	70.0
Min-Max	56-80	60-79	56-80	56-80
Body Mass Index (kg/m**2) #				
<18.5	0	1 (0.1%)	1 (0.1%)	2 (0.1%)
18.5-<25	50 (6.6%)	46 (6.1%)	42 (5.6%)	138 (6.1%)
25-<30	215 (28.4%)	232 (30.7%)	236 (31.2%)	683 (30.1%)
>=30	490 (64.7%)	476 (63.0%)	476 (63.0%)	1442 (63.6%)
Missing	2 (0.3%)	1 (0.1%)	1 (0.1%)	4 (0.2%)
N	755	755	755	2265
Mean	32.9	32.9	32.7	32.8
SD	6.37	6.39	6.23	6.33
Median	32.1	32.1	31.7	32.0
Min-Max	20-64	16-64	17-61	16-64

& Distributed as: allopurinol 200 mg (N=145) plus allopurinol 300 mg (N=611).
@ For categorical variables, p-value is from a Chi-square test.
For continuous variables, p-value is from a one-way analysis of variance using treatment as the factor.
At baseline.

D. Protocol Violations

Sixteen subjects discontinued, prematurely, for reasons of protocol violation. Review of the individual narratives reveals that the majority (10) of protocol violations were due to non-compliance with the protocol and/or the study drug; six additional subjects took prohibited medication.

E. Protocol Amendments

Three protocols were included with the study report for Study F-153: the initial, unamended, protocol, a second which contained one amendment, and, a third which contained both amendments that had been submitted to this NDA. In Section IV (Study Design) the initial (unamended) protocol was summarized. Some of the more significant changes between this initial protocol and the final one (the third protocol) are described here.

The list of prohibited medications was expanded to include metalozone, fenofibrate and indapamide as these were identified as medications that could affect serum urate levels.

In addition, since there are drug-drug interactions between clarithromycin and colchicine, macrolides and ketolides were prohibited for a subject receiving colchicine. Concurrent administration of clopidogrel and naproxen was also prohibited.

The use of NSAIDs and prednisone was clarified.

The visit window for the interval between the Day -4 visit and Day 1/randomization was extended to 7 calendar days. There was additional clarification of the windows for other study visits as well. The timing of rescheduled visits if a subject is having a gout flare at the time of the visit was also clarified.

The original protocol was revised so that the subjects who did not meet laboratory-based inclusion criteria at the Day -4 visit could be retested once within 7 days.

The above changes were summarized in the section of the Final Study Report (Study F-GT06-153) entitled "Protocol Amendment: Summary of Changes." The addition of prohibited medications seems reasonable; each of the medications listed would either raise safety concerns or lead to erroneous results. Other changes appear to clarify ambiguities and, in some cases, to minimize the chance that a subject would be discontinued for a protocol violation (e.g. elongation of a study visit window).

Though not noted specifically as amendments, some additional changes between the initial and final protocol are further noted:

1. In the original protocol randomization was stratified by renal function as defined by creatinine clearance above or below 80 mL/min. For subjects randomized to allopurinol, those with a creatinine clearance between 20 and 79 mL/min were to be given 200 mg of allopurinol while those with a creatinine clearance at or above 80 mL/min were to be given 300 mg of allopurinol. In the final protocol (and the one that was operationalized), subjects were divided into three groups by renal function: those with normal renal function (creatinine clearance above 90 mL/min), those with mild renal impairment (creatinine clearance between 60 and 89 mL/min), and those with moderate renal impairment (creatinine clearance between 30 and 59 mL/min). However, there would still be only two treatment groups in that subjects with normal and mild impairment were to receive allopurinol 300 mg QD while those with moderate renal impairment were to receive allopurinol 200 mg QD. It should also be noted that the exclusion of subjects with severe renal impairment also changed: originally it included subjects with creatinine clearance < 20 mL/min, but, in the amended final version it was expanded to creatinine clearance of < 30 mL/min.

One effect of these changes was to increase the number of patients receiving the higher (300 mg) dose of allopurinol. Since patients with renal impairment frequently receive a reduced and less effective dose of allopurinol, the direction of bias brought about by this change should not have been in favor the study drug, but rather in favor of the active comparator, allopurinol. By raising the cutoff for severe renal impairment (and exclusion

from the study) from a creatinine clearance of 20 to one of 30 mL/min, the protocol effectively minimized the possible risk of adverse events with allopurinol.

2. In the original protocol renal function was the only variable for stratification; in the final protocol, patients were also stratified by their participation in previous long-term studies in this program. Thus, the original protocol would have had two strata, whereas the final protocol had four strata: (did or did not participate in prior trial; moderate renal impairment or normal/mild renal impairment). One advantage of stratifying for previous participation in long-term studies of febuxostat is that it would allow a better assessment of whether the study demonstrated efficacy of febuxostat among febuxostat-naïve patients as well as of patients who had previously received febuxostat. This form of stratification would also allow assessment of safety separately in the two groups to address the concern of whether previous receipt of febuxostat had selected out a group less likely to experience adverse reactions. The stratification would not be expected to contribute bias to the study.

3. In the original protocol lansoprazole was the only proton pump inhibitor (ppi) planned when a subject was given naproxen. In the final protocol a subject was permitted to continue his/her own ppi if it had been used prior to the start of the trial.

F. Study Conduct – Conclusions

Study F-153 appears to have been, in general, conducted in accord with protocol and the stated objectives. Specifically, a systematic bias does not appear to have been introduced via the conduct of the trial.

The trial was carried out at a large number of sites (324) with no single site capable of dictating the results of the study. Despite the large number of sites, only 16 protocol violations (< 1 %) are noted as primary reasons for premature discontinuation.

The three arms of the trial were well balanced both demographically and by medical history.

Premature discontinuations were highest among subjects receiving febuxostat 80 mg daily (21%) and lowest among those receiving febuxostat 40 mg daily (17%); patients receiving allopurinol, the comparator, were in-between with 18% discontinuing prematurely. Analysis of reasons for these discontinuations does not reveal a pattern that is unique to the study drug.

Changes in the protocol from its inception to the final version that was operationalized do not appear to result in any systematic bias that would favor febuxostat.

Overall, this appears to have been a well designed trial that was carried out without significant modification.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Jane Gilbert
1/13/2009 01:52:35 PM
MEDICAL OFFICER

Jeffrey N Siegel
1/19/2009 05:07:18 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-856
Letter Date	July 17, 2008
Stamp Date	July 18, 2008
PDUFA Goal Date	January 18, 2009
Reviewer Name	Jane L. Gilbert, MD, PhD
Review Completion Date	December 14, 2008
Established Name	Febuxostat
Trade Name	Uloric®
Therapeutic Class	Xanthine Oxidase Inhibitor
Applicant	Takeda
Priority Designation	Standard
Formulation	40 mg and 80 mg tablets
Proposed Dosing Regimen	40 or 80 mg each day
Proposed Indication	Hyperuricemia in Patients with Gout
Proposed Intended Population	General Adult

Table of Contents

I. Background

A. Disease

Gout is a crystalline arthropathy predominantly observed in adult men. Symptoms of gout include recurrent inflammatory arthritis that can lead to permanent joint destruction, the development of tophi (nodular collections of monosodium urate crystals) which can be painful when inflamed and limit joint mobility, and uric acid urolithiasis.

Not a rare disease, gout is thought to affect between 3 and 5 million people in the United States. As of 1986, there was a self-reported prevalence of 1.4% in men and 0.6% in women. The prevalence increases with age and has been estimated to reach 9% in men and 6% in women over 80 years of age; gout rarely occurs before adolescence in men and menopause in women. Moreover, various estimates suggest that the incidence of gout has been increasing for, at least, the past 30-40 years. [1]

Gout is the result of hyperuricemia, and though there are individuals with asymptomatic hyperuricemia, there is a strong relationship between elevated uric acid levels and gouty arthritis. Hyperuricemia, which has been called the "cardinal biochemical feature and prerequisite for gout"[2] is defined as a serum urate concentration greater than 7.0 mg/dL. At serum urate levels greater than 7.0 mg/dL, uric acid crystals can precipitate out of solution and deposit in joints and other body tissues where they can produce an inflammatory response. In extremities where body temperatures may be lower, precipitation may occur at a concentration as low as 6.0 mg/dL. In approximately 10% of patients with gout, hyperuricemia results from overproduction of uric acid due to a variety of metabolic derangements or medical disorders such as psoriasis. In approximately 90% of patients, hyperuricemia is the result of underexcretion of uric acid due to alterations in renal function. Regardless of the cause of hyperuricemia, a decrease in the production of uric acid will cause a decrease in the concentration of serum uric acid (sUA). Moreover, lowering the level of sUA is generally associated with a reduction in the frequency of gout attacks. Maintaining sUA at a level of less than 6.0 mg/dL is commonly the target of treatment for chronic gout.

Uric acid is the final product of purine metabolism. The last step in this metabolic pathway involves conversion of xanthine into uric acid by the enzyme xanthine oxidase (XO). Therefore, inhibition of XO provides a well-supported mechanism for reducing uric acid and thereby preventing, or at least reducing the frequency of, gout attacks.

---

[1] John Cush, Clinical Overview of Gout, Arthritis Advisory Committee, November 24, 2008.
[2] Harrison's Principles of Internal Medicine. Thirteenth Edition. p. 2079.

B. Current Treatment

Treatment and prevention of gout currently involve anti-inflammatory medication for acute attacks (e.g., colchicine, corticosteroids or nonsteroidal anti-inflammatories), and uricosurics such as probenecid, or XO inhibitors such as allopurinol for long-term management and prevention. Of these options, the XO inhibitor allopurinol is the most commonly chosen method for treatment of chronic gout.

Allopurinol inhibits XO and in doing so decreases serum urate levels. It is approved at doses up to 800 mg daily and is an effective agent when the dose is titrated to the serum urate level. Prolonged treatment is believed to reduce gouty flares and to lead to the resolution of large tophi. In practice, it is rarely dosed over 300 mg daily and therefore is often ineffective. The side effects of allopurinol include dyspepsia, headache and diarrhea as well as a rash, which occurs in 3%-10% of patients. Allopurinol hypersensitivity syndrome occurs rarely but carries a mortality rate of 20%-30%.

It has long been the practice to reduce the dose of allopurinol in patients with renal impairment (and a decreased creatinine clearance) due to the concern that toxicity may be increased in such patients. Since toxicities develop in the general population on normal doses, it is usually recommended that the dose of allopurinol be reduced for patients with a decreased creatinine clearance (and who therefore have a higher exposure to the drug); this further reduces the efficacy in the population with renal impairment.

Febuxostat is a non-purine selective XO inhibitor which, according to the Applicant, inhibits both oxidized and reduced forms of XO. Applicant contends that febuxostat is at least as potent as allopurinol in general and more efficacious in patients with renal impairment. Febuxostat is proposed for use in the treatment of chronic gout. Two doses are under consideration: 40 mg and 80 mg daily. The proposed label states that "in patients with higher serum uric acid or history/presence of tophi, 80 mg is recommended."

C. Gout and Comorbidities

There is a strong and well-known association between gout and cardiovascular disease. Whether or not this association is attributable to a higher frequency of other common comorbidities such as metabolic syndrome, obesity, or hypertension is less clear. However, the relationship between gout and cardiovascular disease has been confirmed in several large studies. In one analysis of the data from the Framingham study, the risk of coronary heart disease (CHD), myocardial infarction, and angina pectoris was assessed in individuals with and without gout. For men with gout, the two year incidence of CHD was 5.8/1000; the two year incidence of MI was 3.3/1000 and the two year incidence of angina was 3.1/1000. These rates were 1.6, 1.5 and 1.8 times higher than the rate in men

without gout.[3] In a cohort study of 1423 Finnish men, uric acid levels were observed to be a strong predictor of cardiovascular disease:

> ". . . in age-adjusted Cox proportional hazards analyses, serum uric acid levels in the 2 upper thirds were associated with 2.7-fold higher risk of death from CVD than uric acid levels in the lower third. . . . Taking into account cardiovascular risk factors and variables commonly associated with gout . . . increased the relative risk to 3.73 for the upper third vs. the lower third. Further adjustment for factors related to the metabolic syndrome (dyslipidemia, insulin and glucose levels, leisure-time physical activity, and cardiorespiratory fitness) additionally strengthened the risk (relative risk for the upper third vs. lower third 4.77) . . . . Men with uric acid concentrations in the upper third were also more likely to die of coronary heart disease, but the association only trended to significance (32 deaths; relative risk, 3.12 (95% confidence interval 0.92-10.6); ...). Likewise men in the upper third had an increased risk of death from stroke (52 deaths; relative risk, 5.52 (95% confidence interval, 1.09-28.0).....[4]

These studies underscore the fact that in clinical trials the population with gout is likely to represent a group of persons at high risk of CHD.

II. Regulatory History

A. First Cycle

The original NDA 21-856 was submitted to the FDA on December 14, 2004 for febuxostat (Uloric) tablets 80 mg and 120 mg. Review at that time led to a concern about an imbalance in cardiovascular events between study arms with more events observed in the febuxostat than in the control arms. Consequently, an Approvable letter was issued on October 14, 2005. This letter requested that the Applicant "further evaluate the safety profile of Uloric, especially in regard to its potential to result in cardiovascular adverse events." It further stated that the "safety signal may be addressed by providing further comparative controlled clinical safety data or, possibly through reanalyses of the current database."

A second issue raised during the first cycle included a concern about the potential for pharmacokinetic interactions when febuxostat is coadministered with theophylline, azathioprine or mercaptopurine. This issue has been addressed and resolved: labeling will exclude co-administration with these drugs at this time.[5]

---

[3] Abbott, Robert et. al. "Gout and Coronary Heart Disease: The Framingham Study." J Clin Epidemiol. Vol 41, No. 3, pp. 237-242, 1988

[4] Niskanen, Leo K. et. al. Uric Acid Level as a Risk Factor for Cardiovascular and All-Cause Mortality in Middle-Aged Men. Arch Internal Med/vol 164, July 26, 2004.

[5] It is anticipated that Applicant will, at some point, undertake a trial to study the coadministration of febuxostat with theophylline. This may lead to an eventual change in the label.

A third issue concerned the potential for hemorrhagic events with coadministration of warfarin. This issue has been addressed through satisfactory completion of a warfarin interaction study submitted during the third cycle.

Finally, two additional issues involving induction potential of CYP P450 enzymes and dissolution of febuxostat 80-mg and 120-mg tables were raised and have been resolved satisfactorily. (See reviews by Clinical Pharmacology and Chemistry.)

B. Second Cycle

In response to the Approvable letter, the Applicant submitted a Complete Response on February 22, 2006. As part of the Complete Response the Applicant chose to reanalyze existing data augmented by new data from two ongoing long-term extension studies. The studies that formed the basis of this analysis included: C02-009 and C02-010, both of which were Phase 3 randomized controlled trials (RCTs); TMX-00-004, a phase 2 RCT; and, two long term extension studies: C02-021 and TMX 01-005. (More detailed descriptions of these studies can be found in Section III below: Key Trials.)

To address the FDA concern about a possible imbalance in cardiovascular events, the Applicant introduced the use of Antiplatelet Trialists' Collaboration (APTC) endpoints combined with consultation by a cardiologist Dr. William White. The APTC categories were utilized to provide a consistent approach to identifying cardiovascular events. APTC categories were used to evaluate both *investigator-reported* events and, also, to evaluate events *adjudicated* by Dr. White.

To identify investigator-reported events that correspond to APTC categories, MedDRA preferred terms for all adverse events in the database that corresponded to primary and secondary APTC events were identified. Table 1 shows both the types of events that would be categorized as primary and secondary APTC events as well as the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms that were used to identify them.

Table 1: APTC Criteria and Corresponding MedDRA Preferred Terms for the Investigator-Reported Analyses

APTC Criterion	MedDRA Preferred Term	Category
Cardiovascular death	The following MedDRA PTs were associated with cardiovascular death: Acute myocardial infarction Cardiac arrest Cardiac failure congestive Myocardial infarction Retroperitoneal haemorrhage	These events are summarized as **primary APTC events** in this document
Non-fatal myocardial infarction	Acute myocardial infarction[a] Myocardial infarction[a] Silent myocardial infarction[a]	
Non-fatal stroke	Brain stem infarction[a] Cerebrovascular accident[a] Lacunar infarction[a] Cerebral haemorrhage[a]	
Non-fatal cardiac arrest	Cardiac arrest[a]	
Angina	Acute coronary syndrome Angina pectoris Angina unstable	These events are summarized as **secondary APTC events** in this document
Revascularization	Coronary artery atherosclerosis[b] Coronary artery disease[b] Coronary artery occlusion[b] Coronary artery stenosis[b]	
Transient ischemic attack	Transient ischaemic attack	
Venous and peripheral arterial vascular thrombotic events	Pulmonary embolism Deep vein thrombosis Thrombosis Ischaemia	
Non-fatal congestive heart failure	Cardiac failure congestive[b]	

a Only non-fatal events
b Approximately 85% of the reported events also had documentation of revascularization
Source: Complete Response to October 14,2005 Approvable Letter, p. 15.

A second analysis involved blinded adjudication by Dr. William White. In his report, Dr. White states that he reviewed clinical information related to all serious cardiovascular events of a possible cardiovascular nature (n = 113) in the Phase 3 and long-term extension studies. Specifically, describing his methodology, Dr. White writes:

> "In order to provide this type of assessment, lists of all deaths and serious adverse events were reviewed and events with any cardiovascular or cerebrovascular diagnosis were assessed blinded to treatment group and type of study. This process allows for adjudication of the clinical diagnosis using standard criteria for cardiovascular events. This process is particularly useful when a) site investigators do not have clinical expertise in cardiovascular events and/or b) when site investigators were not involved in the management of their study patients during the cardiovascular hospitalization."

Included in the APTC endpoints were the following classes of events: (1) *acute MI*: defined as the presence of 2 of the following: chest pain, abnormal cardiac enzymes or evidence of myocardial injury by EKG; (2) *stroke*: acute hemorrhagic stroke, a focal

neurologic event that lasted for > 24 hours, and (3) *cardiovascular death*: defined as sudden or unexplained deaths or those due to MI, stroke or pulmonary embolus.

Section IV of this document describes in more detail FDA's review of this complete response including the new analyses of APTC events. In brief, FDA reviewers noted an imbalance in certain cardiovascular events. The evidence was, however, not definite in that: (1) very small numbers of cardiovascular events were involved, (2) no consistent dose response was seen, (3) the long-term extension studies had only a limited number of subjects in the active control arm making it difficult to precisely estimate risk in this group, (4) confidence intervals were broad and included values both favorable and unfavorable to febuxostat, and, (5) application of APTC categories and adjudication was introduced in a post hoc fashion. Thus there was uncertainty about whether the findings represented a real increased risk of cardiovascular thromboembolic events with febuxostat. Because of this uncertainty, a second Approvable letter was issued on August 2, 2006. This letter stated that "Before the application may be approved. . . it will be necessary for you to: Provide further data to clarify the cardiovascular risks of the proposed doses and/or provide data on the safety and efficacy of lower doses of febuxostat in order to assure us that a dose level(s) with favorable risk-benefit characteristics has been defined." Since some of the difficulty in reaching a definitive conclusion during the second cycle resulted from post hoc adjudication and reanalysis of data from earlier studies that had not been designed to detect a cardiovascular signal, FDA suggested that the Applicant conduct a new study designed to determine whether the cardiovascular safety signal would be seen again. In discussing the design of such a study the Agency stated that it would be important that the study be designed in such a manner as to collect an adequate number of cardiovascular adverse events to reach conclusions about the cardiovascular safety of febuxostat.

FDA evaluation of the first and second cycle submissions did not contest the efficacy of febuxostat 80 mg. The reason for the Approvable letter, in both cases, was a concern about cardiovascular adverse events. However, FDA did suggest that the Applicant evaluate a lower dose of febuxostat, for which efficacy and safety could be established in a controlled trial.

C. Third Cycle

This is the second resubmission of this NDA and represents the Applicant's response to the Approvable letter of August, 2006.

In this submission the Applicant presents the results of a new trial: F-GT06-153 (F-153), which was designed to evaluate the efficacy and safety of febuxostat 40 mg and 80 mg daily in comparison with allopurinol in subjects with hyperuricemia and gout. This was a larger trial than the previous Phase 3 trials, enrolling 2269 subjects; thus it exceeded the total number of subjects in all previous RCTs. Since it was specifically designed to assess both a lower dose of the drug (febuxostat 40 mg) and to compare this with allopurinol, subjects were randomized 1:1:1 to each of the three arms: febuxostat 40 mg,

febuxostat 80 mg and allopurinol. Randomization was stratified by baseline renal function and whether the subject had completed one of the LTES. The trial was carried out for 6 months. The primary endpoint was the proportion of subjects with a sUA < 6.0 mg/dL at the final visit. Additional endpoints included the proportion of subjects with renal impairment who met the primary endpoint. All subjects who received at least 1 dose of study drug were included in the safety analysis, which was assessed via monitoring of adverse events (AEs), laboratory tests, physical examinations, vital signs, and ECGs.

To address the potential problems involved with post hoc adjudication by a single individual, a three-person, multidisciplinary committee (the Cardiovascular Endpoints Committee) was formed to perform adjudication of potential cardiovascular events. The committee, which included two cardiologists as well as a neurologist, reviewed all deaths and cardiovascular adverse events blinded to treatment group. APTC events were prespecified and included: cardiovascular death (including sudden death), non-fatal MI, and non-fatal stroke. Non-APTC events included: unstable angina, coronary revascularization, TIA, cerebral revascularization, venous and peripheral arterial vascular thrombotic events, congestive heart failure, arrhythmia (without evidence of ischemia) and other events. If committee members did not agree upon the classification of an event, it was discussed and ultimately decided by a simple majority vote. If an event could not be classified, even after additional information had been requested from study sites, the event was classified as "insufficient data."

This process resulted in the committee evaluating 319 events (almost three times the number adjudicated in previous trials where 113 were evaluated). Additional details describing study F-153 and the analysis of it can be found in Sections III and V below.

III. Key Trials

A. Randomized Controlled Trials:

C02-009. This was a 28-week, Phase 3, randomized, double-blind placebo and active-controlled study in which febuxostat 80 mg, 120 mg, or 240 mg daily was studied and compared with allopurinol (100/300 mg depending upon renal function) daily. A total of 1072 subjects were randomized and on a daily basis received at least 1 dose of drug: 134 received placebo, 267 received febuxostat 80 mg, 269 received febuxostat 120 mg, 134 received febuxostat 240 mg and 268 received allopurinol 300/100 mg.

C02-010. This was a 52-week, Phase 3, randomized double-blind, active-controlled study in which febuxostat 80 mg, febuxostat 120 mg and allopurinol 300 mg were studied. A total of 760 patients were randomized and received at least one dose of study drug on a daily basis: 256 received febuxostat 80 mg, 251 received febuxostat 120 mg and 253 received allopurinol 300 mg.

TMX-00-004. This was a 28-day, Phase 2, placebo-controlled, dose-response study in which 153 subjects with hyperuricemia were randomized to receive either placebo or febuxostat 40 mg, 80 mg or 120 mg daily.

F-GT06-153. This was a 6-month Phase 3, randomized, double-blind active controlled study designed to evaluate the efficacy and safety of febuxostat 40 mg and 80 mg daily compared with allopurinol. A total of 2269 subjects were enrolled and randomized 1:1:1 to the three arms. Randomization was stratified by baseline renal function and whether they had completed study TMX-01-005 or C02-021. This study was developed in response to FDA's concern about a possible cardiovascular safety signal and was prospectively designed to address that issue.

B. Long-Term Extension Studies:

C02-021. A total of 1086 subjects were enrolled in this Phase 3 open-label long-term extension study. All subjects had completed either Studies C02-009 or C02-010. Subjects were originally assigned to receive febuxostat 80 mg daily but the dose was increased to 120 mg or decreased to 40 mg based upon serum urate levels, adverse events or the investigator's discretion. An allopurinol control group was added in an amendment and subjects who entered under this amendment were randomized to either allopurinol, febuxostat 80 mg or febuxostat 120 mg in a 1:2:2 ratio. Subjects on febuxostat could titrate their doses upward or downward based on serum uric acid level. Also, subjects randomized to febuxostat or allopurinol could change drug based upon serum urate level, adverse events or at the investigator's discretion. A total of 351 subjects enrolled before and 735 subjects enrolled after the amendment that added allopurinol and randomization.

TMX-01-005. This was a Phase 2, open-label, 5-year extension study enrolling 116 subjects who had previously completed TMX-01-004 (the four week dose ranging study). Subjects initially received febuxostat 80 mg daily but based on serum urate level, tolerance or at the investigator's discretion, the dose was titrated up to 120 mg or down to 40 mg.

IV. Second Cycle

A. Overview

As described above, upon review of the original submission, the FDA determined that there was an imbalance in the number of serious cardiovascular adverse events in febuxostat arms as compared to control arms. As a result the Agency issued an Approvable letter requesting additional data or a reanalysis of the available data to address this potential risk. A Complete Response to the Approvable letter was submitted on 2/22/06. To address the concern of the FDA regarding the potential risk of cardiovascular-thromboembolic adverse events, the Applicant performed several new analyses of the data concerning cardiovascular events. This included a reanalysis of existing data based upon the Antiplatelet Trialists' Collaboration (APTC) endpoints; it also included a post hoc adjudication by Dr. White, a cardiologist. All serious adverse events were adjudicated in a blinded fashion by Dr. William White. The analysis of

APTC events (adjudicated and non-adjudicated) was undertaken separately for phase 3 studies and long-term studies.

B. FDA Review of February, 2006 Complete Response

FDA's review of the Complete Response of 2006 concluded that the data continued to demonstrate a safety signal with febuxostat. This section will outline and present data describing the categories of events that resulted in this conclusion.

1. All cause mortality

Review of the deaths occurring in the febuxostat clinical development program revealed that all deaths were seen in febuxostat-treated patients. As shown in Table 2, there were 4 deaths in RCTs and 8 in long-term extension studies (LTES). All were in febuxostat-treated patients and none were in the allopurinol arm. The mortality rate, in RCTs, was 0.60/ 100 patient years among febuxostat-treated patients. In the LTES the mortality rate was actually somewhat lower: 0.38/ 100 patient years for febuxostat-treated patients.

Table 2: All-Cause Mortality in Febuxostat Clinical Program by Patient-Years of Exposure with Data as of 08 February 2006

Treatment	Patient-Years of Exposure	Number of Deaths	Rate Per 100 Patient-Years	95% Confidence Interval
Phase 3 Randomized Controlled Studies				
Febuxostat Total	671	4	0.60	0.162-1.526
Allopurinol 300/100 mg QD	334	0	0.0	0.000-1.105
Long-Term Extension Studies				
Febuxostat Total	2121	8	0.38	0.163-0.743
Allopurinol 300/100 mg QD	145	0	0.0	0.000-2.538
Phase 3 Randomized Controlled and Long-Term Extension Studies				
Febuxostat Total	2792	12	0.43	0.222-0.751
Allopurinol 300/100 mg QD	479	0	0.0	0.000-0.770

Note: No subjects died in the Phase 1 studies or during treatment in the Phase 2 controlled clinical trial (TMX-00-004).
The confidence intervals are calculated based on Poisson distribution.

Source: FDA Clinical Review, July 2006

Although mortality is higher in the febuxostat arm, the small numbers involved make it difficult to reach a definite conclusion.

2. Cardiovascular Mortality.

Turning to the cause of death, further analysis reveals that 9 of the 12 deaths in the febuxostat arm were attributable to cardiovascular causes. Table 3 presents the results from the analysis of RCTs and the LTES. Of the 9 deaths in the febuxostat arm, 3 were in the RCTs and 6 were in the LTES. Though there were no deaths at all, cardiovascular or otherwise, in the allopurinol arm, it must be noted that exposure to allopurinol was quite limited (479.1 patient years) compared with febuxostat (2791.8 patient years). This difference in exposure was due to the fact that most subjects in the open-label, long-term extension studies were treated with febuxostat.

Table 3: Updated Cardiovascular Deaths in Combined Phase 3 Randomized Controlled and Long-Term Extension Studies with Data as of 08 February 2006

	Treatment						
	Placebo	Febuxostat					Allopurinol
Number of CV	(N=134) (PY=59.9)	Total (N=1692) (PY=2791.8)	40 mg (N=12) (PY=34.6)	80 mg (N=1221) (PY=1697.1)	120 mg (N=909) (PY=1006.1)	240 mg (N=134) (PY=54.0)	300/100 (N=642) (PY=479.1)
Deaths	0	9	0	5	4	0	0
Per 100 PY	0	0.32	0	0.29	0.40	0	0
95%CI[a]	(0–6.16)	(0.147-0.612)	(0–10.67)	(0.096-0.688)	(0.108-1.02)	(0–6.83)	(0-0.77)

Studies included: TMX-01-005, C02-009, C02-010, and C02-021.

a 95% CI were calculated based on Poisson distribution.

Source: FDA Clinical Review, July 2006

3. Serious Adverse Events (SAEs).

Examination of the Phase 3 and Long Term Extension studies revealed that SAEs were more common in febuxostat-treated patients compared with allopurinol-treated patients in the phase 3 randomized controlled studies (Table 4). However, in long-term extension studies, SAEs in the allopurinol group were more common than in febuxostat-treated patients.

Table 4: Incidence of Serious Adverse Events per 100 Patient-Years of Exposure in Long-Term Extension Studies and Phase 3 Randomized Controlled Studies

Treatment Emergent SAEs per 100 PY							
Long Term Extension Studies		Febuxostat					
		Total N=1143 PY=1933.7	**40 mg QD** N=12 PY=33.0	**80 mg QD** N=910 PY=1265.4	**120 mg QD** N=522 PY=635.3		**Allopurinol** 300/100 QD N=178 PY=133.3
Phase 3 Randomized Controlled Studies	**Placebo** N = 134 PY =59.9	**Total** N=1177 PY=671.1		**80 mg QD** N=523 PY= 312.6	**120 mg QD** N=520 PY =304.5	**240 mg QD** N=134 PY =304.5	**Allopurinol** 300/100 QD N=521 PY=333.7
Long-Term		9.5	21.2	9.9	8		11.2
Phase 3	5	11.6		11.8	11.5	11.1	8.1

SAE = serious adverse event, PY = patient-years of exposure
Long term extension studies include: TMX-01-005 and C02-010; phase 3 randomized controlled studies include: C02-009 and C09-010.
Source: FDA Clinical Review, July 2006

Examination of individual SAEs did not indicate a pattern of increased rate of SAEs in any particular category for febuxostat with the exception of the category of ischemic coronary artery disease. For that category, which included MI, angina pectoris, angina unstable and MI, the rates were 1 event per 100 patient-years for febuxostat-treated subjects compared with 0.8 events per 100 patient years in the allopurinol arm.

4. Cardiovascular SAEs.

To further investigate the risk of serious cardiovascular thromboembolic events the Applicant employed a standard method of categorization based upon the endpoints established by the Antiplatelet Trialists' Collaboration (APTC). Two types of analyses were undertaken. The first analysis explored and categorized investigator-reported events (see Table 1). The second analysis utilized a post-hoc analysis performed by a single cardiologist who adjudicated adverse events as to whether or not they were compatible with APTC endpoints.

a. Investigator-reported APTC events

Investigator-reported events were divided into primary and secondary APTC events. As shown in Table 1, primary APTC events include cardiovascular death, non-fatal MI, non-fatal stroke, and non-fatal cardiac arrest. Secondary APTC events include angina, revascularization, TIA, venous and peripheral arterial vascular thrombotic events and non-fatal congestive heart failure. Table 5 summarizes investigator-reported primary APTC events in the randomized-controlled phase 3 trials.

Table 5

Investigator-Reported Primary APTC Events: RCTs, N (%)						
Primary APTC Events	***Placebo***	***Febuxostat***				***Allopurinol***
		Total	80 mg	120 mg	240 mg	300/100 mg
	N=134	N=1177	N=523	N=520	N=134	N=521
Overall	**0**	**9 (0.8)**	**4 (0.8)**	**5 (1.0)**	**0**	**1 (0.2)**
CV Death	0	3 (0.3)	2 (0.4)	1 (0.2)	0	0
Non-fatal MI	0	5 (0.4)	2 (0.4)	3 (0.6)	0	1 (0.2)
Non-fatal stroke	0	1 (0.1)	0	1 (0.2)	0	0
Non-fatal cardiac arrest	0	1 (0.1)	0	1 (0.2)	0	0

Source: Complete Response to October 14, 2005 Approvable Letter

The incidence of investigator-reported APTC events is numerically higher in the febuxostat group compared with the allopurinol group: among febuxostat-treated patients there were 9 events (0.8 %) while in the allopurinol group there was only one event (0.2%). In order to compare the two treatment groups, we calculated the risk ratio (by dividing the rates between the two treatment groups) and, also, the 95% confidence interval (using the binomial distribution). The risk ratio between the two treatment groups is 4 with a 95% CI of (0.5, 32). The confidence interval includes the null value and values that correspond to a more favorable as well as a less favorable outcome with febuxostat compared to allopurinol. Consequently, the direction of the difference in risk, if any, is not known with much confidence.

Table 6 summarizes investigator-reported primary APTC events in the long-term extension studies.[6] The overall rate of investigator-reported APTC events is higher in the febuxostat group compared with the allopurinol group (1.5 versus 0.75 events/100 pt-years, respectively).

[6] This table, drawn from the previous FDA review, differs from that originally provided by the Applicant due to the fact that the.FDA review resulted in adjudication of an additional event in the Febuxostat 120 mg arm.

Table 6: Treatment-Emergent Primary APTC Events per 100 Patient-Years of Exposure in the Long-Term Extension Studies

Primary APTC Events	Treatment group				
	Febuxostat				Allopurinol
	Total N=1143 PY=1933.7	**40 mg QD** N=12 PY=33.0	**80 mg QD** N=910 PY=1265.4	**120 mg QD** N=522 PY=635.3	**300/100 mg QD** N=178 PY=133.3
Overall 95% CI	29 (1.50) (0.96-2.09)	1 (3.0) (0.077-16.89)	18 (1.4) (0.84-2.25)	10 (1.57) (0.65-2.69)	1 (0.75) (0.019-4.18)
CV death 95% CI	5 (0.26)	0 (0-11.2)	1 (<0.1) (0.002-0.44)	4 (0.63)	0 (0-2.77)
Non-fatal MI 95% CI	15 (0.8) (0.43-1.28)	0 (0-11.2)	12 (0.9) (0.490-1.66)	3 (0.5) (0.097-1.38)	1 (0.8) (0.19-4.18)
Non-fatal stroke 95% CI	9 (0.5) (0.21-0.884)	1 (3.0) (0.077-16.9)	5 (0.4) (0.128-0.922)	3 (0.5) (0.097-1.38)	0 (0-2.77)

N=number of subjects dosed; PY-patient year
Studies included: C02-021 and TMX-01-005
Source: FDA Clinical Review, July, 2006.

Table 7 displays the incidence of cardiovascular thromboembolic events using the more inclusive criteria of investigator-reported primary *and* secondary APTC events. Events were observed more frequently with febuxostat than with allopurinol. The most common events in the febuxostat group were angina, revascularization and non-fatal MI. Except for revascularization, all events were more common with febuxostat compared to allopurinol and placebo.

Table 7: Primary and Secondary Investigator-Reported APTC Events in the Phase 3 Randomized Controlled Studies

Primary and Secondary APTC Events	Treatment Group, n (%)					
	Placebo	Febuxostat				Allopurinol
		Total	80 mg QD	120 mg QD	240 mg QD	300/100 mg QD
	(N=134)	(N=1177)	(N=523)	(N=520)	(N=134)	(N=521)
Overall 95% CI[a]	1 (0.7) (0.019-4.09)	25 (2.1) (1.38-3.12)	13 (2.5) (1.33-4.21)	11 (2.1) (1.06-3.75)	1 (0.7) (0.019-4.09)	7 (1.3) (0.54-2.75)
CV death	0	3 (0.3)	2 (0.4)	1 (0.2)	0	0
Non-fatal myocardial infarction	0	5 (0.4)	2 (0.4)	3 (0.6)	0	1 (0.2)
Non-fatal stroke	0	1 (<0.1)	0	1 (0.2)	0	0
Non-fatal cardiac arrest	0	1 (<0.1)	0	1 (0.2)	0	0
Angina	0	6 (0.5)	4 (0.8)	1 (0.2)	1 (0.7)	2 (0.4)
Revascularization	1 (0.7)	6 (0.5)	4 (0.8)	2 (0.4)	0	4 (0.8)
Transient Ischemic Attack	0	2 (0.2)	2 (0.4)	0	0	0
Venous and peripheral arterial vascular thrombotic events	0	2 (0.2)	0	2 (0.4)	0	0
Non-fatal congestive heart failure	0	3 (0.3)	2 (0.4)	1 (0.2)	0	1 (0.2)

Studies included: C02-009 and C02-010

a CI calculated based on binomial distribution

Source: Complete Response to October 14, 2005 Approvable Letter

b. Adjudicated APTC events

In order to confirm that adverse events were accurately categorized as cardiovascular thromboembolic events the Applicant recruited a cardiologist, Dr. White, to examine the case reports in a blinded fashion and to determine which cases truly met APTC endpoints. The results of this reanalysis constitute the set of adjudicated APTC events.

As shown in Table 8, below, there were 7 adjudicated APTC events, compared with 10 investigator-reported APTC events, in the randomized controlled studies. Three of the investigator-reported events were adjudicated to be "non-APTC" by Dr. White.

Table 8: Percentages of Subjects with Treatment-Emergent Adjudicated APTC Events in the Phase 3 Randomized Controlled Studies

	Treatment Group					
	Placebo	Febuxostat				Allopurinol
		Total	80 mg QD	120 mg QD	240 mg QD	300/100 mg QD
	(N=134)	(N=1177)	(N=523)	(N=520)	(N=134)	(N=521)
APTC Events						
Number of Subjects	0	7	4	3	0	1
Rate (%)	0	0.59	0.76	0.58	0	0.19
95% CI[a]	(0.00-2.71)	(0.239-1.22)	(0.209-1.95)	(0.119-1.68)	(0.00-2.71)	(0.005-1.07)
CV Death						
Number of Subjects	0	3	2	1	0	0
Rate (%)	0	0.25	0.38	0.19	0	0
95% CI[a]	(0.00-2.71)	(0.053-0.743)	(0.046-1.37)	(0.005-1.07)	(0.00-2.71)	(0.00-0.706)
Non-fatal MI						
Number of Subjects	0	4	2	2	0	1
Rate (%)	0	0.34	0.38	0.38	0	0.19
95% CI[a]	(0.00-2.71)	(0.093-0.868)	(0.046-1.37)	(0.047-1.38)	(0.00-2.71)	(0.005-1.07)

Studies included: C02-009 and C02-010

a The confidence intervals are calculated based on binomial distribution

Source: Complete Response to October 14, 2005 Approvable Letter , p. 39.

Despite this reduction in the number of events, the proportion of events in the febuxostat 80 mg group remains approximately four times that of allopurinol (95% CI 0.4, 36); the proportion in the febuxostat 120 mg group remains approximately 3 times that of allopurinol (95% CI 0.3, 29). The wide confidence intervals include values that correspond to a more (as well as a less) favorable outcome with febuxostat compared to allopurinol. The direction of the difference in risk, if any, is therefore not known with much confidence.

Table 9 summarizes the adjudicated APTC events in long-term extension studies. The overall rate of primary adjudicated APTC events in long-term extension studies is higher in the febuxostat group compared to the allopurinol group. However, one should note, as before, the limited exposure to allopurinol in this group.

Table 9: Incidence of Treatment-Emergent Adjudicated APTC Events per 100 Patient-Years of Exposure in the Long-Term Extension Studies

	Treatment Group				
	Febuxostat				Allopurinol
	Total (N=1143) (PY=1933.7)	40 mg QD (N=12) (PY=33.0)	80 mg QD (N=910) (PY=1265.4)	120 mg QD (N=522) (PY=635.3)	300/100 mg QD (N=178) (PY=133.3)
APTC Events					
Number of Subjects	21	1	12	8	1
Rate per 100 PY	1.09	3.03	0.95	1.26	0.75
95% CI[a]	(0.672-1.66)	(0.077-16.9)	(0.490-1.65)	(0.544-2.48)	(0.019-4.18)
CV Death					
Number of Subjects	4	0	1	3	0
Rate per 100 PY	0.21	0	0.08	0.47	0
95% CI[a]	(0.056-0.530)	(0-11.2)	(0.002-0.440)	(0.097-1.38)	(0-2.77)
Non-fatal MI					
Number of Subjects	9	0	7	2	1
Rate per 100 PY	0.47	0	0.55	0.31	0.75
95% CI[a]	(0.213-0.884)	(0-11.2)	(0.222-1.14)	(0.038-1.14)	(0.019-4.18)
Non-fatal Stroke					
Number of Subjects	8	1	4	3	0
Rate per 100 PY	0.41	3.03	0.32	0.47	0
95% CI[a]	(0.179-0.815)	(0.077-16.9)	(0.086-0.809)	(0.097-1.38)	(0-2.77)

Studies included: TMX-01-005 and C02-021

a The confidence intervals are calculated based on Poisson distribution

Source: Complete Response to October 14, 2005 Approvable Letter, p.44.

C. *Summary, Second Cycle*

Several analyses in the FDA review of the Complete Response of 2006 suggested that cardiovascular adverse events occur more frequently in patients treated with febuxostat compared to patients treated with allopurinol. In the controlled trials there was a higher rate of all cause and cardiovascular mortality among patients receiving febuxostat. In addition there was a higher rate of cardiovascular-thromboembolic SAEs as measured by both investigator-reported and adjudicated APTC events.

Although a concern was raised about cardiovascular safety, there were limitations in the data that raised uncertainty about the conclusions. First, many of the comparisons involved small numbers of events. Second, exposure to allopurinol in the LTES was limited since most patients in the LTES received open-label febuxostat. That is, the long-term extension studies included 178 persons with 133.3 patient-years of exposure in the allopurinol arms compared to 1143 persons in the febuxostat arms with 1933.7 patient-years of exposure.

While the disproportionate number of deaths and cardiovascular-thromboembolic events in the febuxostat group suggests that febuxostat may be associated with an increased cardiovascular risk, the limitations described above made it difficult to reach firm conclusions. Thus, the FDA determined that febuxostat could not be approved without additional clinical trial data to assess cardiovascular risk.

V. Third Cycle: Study F-GT 06-153 (F-153)

A. Study Design

The principle feature of the third cycle review is a new six-month, Phase 3 RCT (F-GT06-153) to evaluate the safety and efficacy of febuxostat 40 mg and 80 mg, in comparison with allopurinol (300 mg or 200 mg)[7] in subjects with gout and hyperuricemia. Patients, who were stratified by renal function, were randomized 1:1:1 to each of the three arms.

Subjects selected for this multicenter study included males and females between 18 and 85 years of age with a history or presence of gout. It was required that each subject have a sUA>8.0 mg/dL at the time of the study visit four days before start of the study.

The primary endpoint was achievement of a sUA < 6 mg/dL at the final visit. In Study F-153, a non-inferiority criterion was used to assess the efficacy of febuxostat 40 mg since this dose was expected to be similar in activity to allopurinol but not necessarily superior. The study was designed using a 10% inferiority margin; that is to say, to rule out that febuxostat 40 mg was more than 10% inferior to allopurinol. The rationale for the choice of a non-inferiority margin is based on a response rate of 0% to 1% in placebo controls (see Table 12) and 36% to 42% with allopurinol indicating that the effect size of allopurinol is 35-41%. Thus, a 10% non-inferiority margin assures that at least three-quarters (30/40) of the effect size of the active control is maintained.

The primary analysis was based on the ITT population; defined as all randomized subjects who had received at least one dose of the drug.

The third cycle also includes evaluation of an additional 12 months of exposure in the two long-term extension studies: TMX-01-005 and C02-021.

B. Study Conduct

A total of 2269 subjects were enrolled. At least 65% of the subjects in this study had mild-to-moderate renal impairment (with creatinine clearance of 30-89 mL/min).

Demographic data as well as pertinent medical history for enrollees is given in Table 10. No clinically significant imbalances between study arms were noted.

[7] Whether they received 300 mg or 200 mg of allopurinol was determined by baseline renal function.

Table 10: Demographic Data and Medical History by Treatment Arm in study F-GT06-153.

Variable	Treatment Group n (%)			
	Febuxostat 40 mg QD (N=757)	Febuxostat 80 mg QD (N=756)	Allopurinol 300/200 mg QD (N=756)	All Subjects (N=2269)
Gender				
Male	722 (95.4)	710 (93.9)	709 (93.8)	2141 (94.4)
Female	35 (4.6)	46 (6.1)	47 (6.2)	128 (5.6)
Race				
American Indian or Alaska Native	6 (0.8)	10 (1.3)	6 (0.8)	22 (1.0)
Asian	26 (3.4)	25 (3.3)	37 (4.9)	88 (3.9)
Black or African American	83 (11.0)	78 (10.3)	67 (8.9)	228 (10.0)
Native Hawaiian or Other Pacific Islander	11 (1.5)	10 (1.3)	11 (1.5)	32 (1.4)
White	620 (81.9)	618 (81.7)	625 (82.7)	1863 (82.1)
Other	11 (1.5)	15 (2.0)	8 (1.1)	34 (1.5)
Missing	0	0	2 (0.3)	2 (0.1)
Ethnicity				
Hispanic or Latino	47 (6.2)	49 (6.5)	53 (7.0)	149 (6.6)
Not Hispanic or Latino	710 (93.8)	707 (93.5)	702 (92.9)	2119 (93.4)
Missing	0	0	1 (0.1)	1 (0.0)
Age (yr)				
Mean ± SD	52.5±11.68	53.0±11.79	52.9±11.73	52.8±11.73
Range	21-85	21-85	19-85	19-85
Weight (lb)				
Mean ± SD	229.9±48.58	227.3±47.70	225.5±46.09	227.6±47.48
Range	117-449	102-474	102-425	102-474
Height (in)				
Mean ± SD	70.0±3.29	69.7±3.31	69.6±3.32	69.8±3.31
Range	56-80	60-79	56-80	56-80
Body Mass Index (kg/m²)				
Mean ± SD	32.9±6.37	32.9±6.39	32.7±6.23	32.8±6.33
Range	20-64	16-64	17-61	16-64
Baseline Serum Urate (mg/dL)				
Mean ± SD	9.6±1.15	9.6±1.20	9.5±1.19	9.6±1.18
Range	8-14	8-15	8-15	8-15
Completed Previous Febuxostat Study TMX-01-005/C02-021	98 (12.9)	88 (11.6)	90 (11.9)	276 (12.2)
Medical History				
Renal Function Moderately Impaired[a]	130 (17.2)	136 (18.0)	136 (18.0)	402 (17.7)
Renal Function Mildly Impaired[b]	349 (46.1)	367 (48.5)	365 (48.3)	1081 (47.6)
Renal Function Normal[c]	278 (36.7)	253 (33.5)	255 (33.7)	786 (34.6)
Kidney Stone	104 (13.7)	121 (16.0)	104 (13.8)	329 (14.5)
Diabetes	89 (11.8)	113 (14.9)	110 (14.6)	312 (13.8)
Hypercholesterolemia	52 (6.9)	53 (7.0)	57 (7.5)	162 (7.1)
Hyperlipidemia	299 (39.5)	308 (40.7)	335 (44.3)	942 (41.5)
Hypertension	388 (51.3)	402 (53.2)	409 (54.1)	1199 (52.8)

a Moderately impaired: baseline estimated creatinine clearance (ECC) 30 mL/min to 59 mL/min.
b Mildly impaired: ECC 60 mL/min to 89 mL/min.
c Normal: ECC ≥90 mL/min.

Source: Clinical Study Report F-GT06-153, Synopsis.

Table 11 summarizes the disposition of subjects. While there is a higher rate of premature discontinuation among those in the febuxostat 80-mg arm, there does not seem to be any single reason that accounts for this; specifically with reference to adverse events, the number (and %) is approximately the same in the febuxostat 80 mg and allopurinol arms: 61 (8.1%) compared with 64 (8.5%) in allopurinol.

Table 11: Premature Discontinuation by Treatment Arm in Study F-GT06-153

Variable	Treatment Group n (%)		
	Febuxostat 40 mg QD	Febuxostat 80 mg QD	Allopurinol 300/200 mg QD
Number of Subjects Enrolled	**N = 757**	**N = 756**	**N = 756**
Number of Subjects Prematurely Discontinued	**125 (16.5)**	**158 (20.9)**	**135 (17.9)**
Primary Reason for Premature Discontinuation			
Adverse Events	49 (6.5)	61 (8.1)	64 (8.5)
Protocol Violation	10 (1.3)	2 (0.3)	4 (0.5)
Personal reasons(s)	12 (1.6)	24 (3.2)	9 (1.2)
Lost to Follow-Up	28 (3.7)	33 (4.4)	28 (3.7)
Therapeutic Failure	1 (0.1)	1 (0.1)	1 (0.1)
Withdrew Consent	14 (1.8)	20 (2.6)	16 (2.1)
Did not Meet Inclusion/Exclusion Criteria	0	2 (0.3)	0
Gout Flare	3 (0.4)	7 (0.9)	2 (0.3)
Other	8 (1.1)	8 (1.1)	11 (1.5)

Source: Clinical Study Report F-GT06-153, Synopsis.

C. *Efficacy*

Data in Study F-153 show that 67% of enrollees receiving febuxostat 80 mg meet the primary endpoint. This compares with 42% of subjects who received allopurinol. These data also reveal that a similar proportion of patients receiving febuxostat 40 mg and allopurinol achieved a sUA< 6.0 mg/dL: 45% in the febuxostat group and 42% in the allopurinol group. Accordingly, febuxostat 40 mg is non-inferior to allopurinol by the prespecified criteria. (See **Table 12**)

Efficacy results for all four RCTs are further summarized in **Table 12.** In all four trials 67%-76% of subjects treated with febuxostat 80 mg daily achieved the primary endpoint of a sUA < 6.0 mg/dL. In the three RCTs where allopurinol was a comparator, these results demonstrate superiority of febuxostat 80 mg to allopurinol at a statistically significant level.

Table 12

Efficacy: Proportion with sUA<6 mg/dL at Final Visit				
Study	**Febuxostat 40 mg**	**Febuxostat 80 mg**	**Allopurinol 300 mg**	**Placebo**
F-153	45% ‡ (342/757)	67% * (507/756)	42% (318/755)	N/A
C02-009	N/A	72%* (183/253)	39% (102/263)	1% (1/127)
C02-010	N/A	74%* (185/249)	36% (88/242)	N/A
TMX-004	56% (19/34)	76% (28/37)	N/A	0% (0/35)

Source: Complete Response to August 2006 Approvable Letter
* Indicates statistical significance versus allopurinol at p<0.001.
‡ Noninferior to allopurinol using the lower bound of the 95% confidence interval of the difference (-1.9%) being greater thanthe critical value of -10%.

Since patients with more (or less) severe manifestations of gout may respond differently to febuxostat, it is useful to consider subjects with different levels of baseline sUA. Table 13 presents a comparison of subjects with sUA above or below 10 mg/dL. (Recall that all subjects enrolled had a sUA > 8 mg/dL.) Examination of the results reveals that febuxostat is generally less efficacious for those with the higher level of urate: for the 40-mg dose of febuxostat, only 27% of subjects with a sUA $\geq$ 10 mg/dL meet the primary endpoint compared with 54% of subjects with a sUA < 10 mg/dL. For the 80-mg dose of febuxostat, over 2/3 of all subjects meet the primary endpoint, compared with only 49% of those with a serum urate over 10 mg/dL.

Table 13: Proportion of Subjects in F-153, by Level of Serum Urate, who meet the Primary endpoint of a sUA < 6 mg/dL

	All subjects	sUA<10 mg/dL	sUA≥10 mg/dL
Allopurinol	**42%** *n=756*	**47%** *n=526*	**31%** *n=230*
Febuxostat 40 mg	**45%** *n=757*	**54%** *n=508*	**27%** *n=249*
Febuxostat 80 mg	**67%** *n=756*	**76%** *n=502*	**49%** *n=254*

Source: Takeda, Arthritis Advisory Committee Meeting, 11/24/2008.

Patients with renal impairment constitute another group requiring special consideration. There are two reasons to do this. First, at least some patients with renal impairment are currently undertreated due to the usual and customary practice of reducing allopurinol according to creatinine clearance. Second, while febuxostat is largely metabolized by the liver, there is some renal metabolism. Consequently, the exposure to febuxostat is higher among those with renal impairment compared to those with normal renal function.

Recognizing the importance of the subgroup with renal impairment, the Applicant has defined a secondary endpoint of Study F-153 as the proportion of subjects with renal impairment whose final visit sUA is < 6.0 mg/dL. For purposes of this study, patients were categorized as having mild renal impairment if their baseline estimated creatinine clearance was between 60 and 89 mL/min; moderate impairment involved an estimated creatinine clearance of 30 to 59 mL/min. Patients were categorized as having normal renal function if the creatinine clearance was ≥ 90 mL/min. In Study F-153, 402 subjects, or 18% had moderate renal impairment, 1081 or 48% had mild impairment and 786, or 35% were categorized as having normal renal function. Table 14 summarizes results for those subjects with renal impairment. A higher proportion of subjects treated with both febuxostat 40-mg and 80-mg doses achieved sUA< 6.0 mg/dL compared to subjects in the allopurinol group. Also, a higher proportion of subjects in the febuxostat 80-mg arm met the secondary endpoint than those in the febuxostat 40-mg arm.

Table 14

Efficacy: Proportion of Moderate/Mild Renally Impaired Subjects with sUA< 6.0 mg/dL at Final Visit*

	Febuxostat 40 mg	Febuxostat 80 mg	Allopurinol 300/200 mg
	N=479	N=503	N=501
sUA<6.0 mg/dL	**238 (50%)**	**360 (72%)**	**212 (42%)**
	Difference in Proportions	95% CI	p-value
Feb 40 vs Allo	7%	(1%, 14%)	0.021
Feb 80 vs Allo	29%	(23%, 35%)	<.001
Feb 40 vs Feb 80	22%	(16%, 28%)	<0.001

Source:Complete Response to August 2006 Approvable Letter

*No multiple adjustments for multiple comparisons were performed on this secondary variable.

In summary, in randomized controlled trials a greater proportion of subjects achieved a sUA less than 6.0 mg/dL with febuxostat 80 mg than with allopurinol, and this difference was statistically significant. Febuxostat 40 mg was demonstrated to be similar to (i.e., statistically non-inferior to) allopurinol.

Compared to the total study population, patients with higher levels of serum uric acid (sUA $\geq$ 10 mg/dL) achieve a sUA < 6 mg/dL less frequently (e.g., 49% vs 67% for those receiving the 80-mg dose of febuxostat).

Finally, for patients with renal impairment, a greater proportion of subjects in both febuxostat 40-mg and 80-mg treatment regimens achieved sUA less than 6.0 mg/dL compared to subjects in the allopurinol group.

D. Safety

Review of the data submitted during the second cycle suggested that febuxostat treatment may be associated with a higher risk of cardiovascular-thromboembolic events. The data from the following categories of adverse events were reviewed and the results indicated that a higher proportion of patients in the febuxostat group experienced these adverse events compared to patients in the allopurinol group:

All cause mortality
Cardiovascular mortality
Investigator reported primary APTC events (RCTs)
Investigator reported primary APTC events (LTES)
Investigator reported primary and secondary APTC events
Adjudicated APTC events (RCTs)
Adjudicated APTC events (LTES)

However, as discussed above, uncertainties in the data did not allow definite conclusions.

To assess whether a cardiovascular safety signal was confirmed by additional information, the data from the new RCT, Study F-153, were reviewed as well as data from the ongoing LTES.

The new trial, Study F-153, was designed to determine whether, in a larger study, the cardiovascular safety signal seen previously would be seen again. It is, in total, larger than the other two Phase 3 trials combined: 2269 subjects in Study F-153 compared with 1832 in C02-009 and C02-010 combined. Second, the number of subjects randomized to the active control arm, allopurinol, is approximately three times the number randomized in the other two trials: 756 subjects in Study F-153 vs 268 and 253 subjects in each of the earlier studies. The study included patients at risk for cardiovascular disease: approximately 1300 subjects with a prior cardiac history disease were enrolled. Finally, the cardiovascular endpoints were prespecified. However, as described below, only a modest number of cardiovascular events were seen in the trial.

1. All Cause Mortality

In the previous Phase 3 trials more deaths were seen in the febuxostat arms than in the control arms (see Table 2). In Study F-153 (see Table 15) there were numerically more deaths in the allopurinol arm than in either febuxostat arm (3 with allopurinol vs. 1 in each of the febuxostat arms). The 95% CIs for the relative risk between the allopurinol and febuxostat arms include the null value and values that correspond to a more (as well as a less) favorable outcome with febuxostat than with allopurinol; consequently, the direction of the difference in risk, if any, is not known with much confidence. These data do not provide evidence of an elevated risk of all cause mortality for febuxostat in the new F-153 study.

Table 15: Analyses of All Mortality. Study F-GT06-153.

Variable	Febuxostat 40 mg QD (N=757) (PY=343.5)	Febuxostat 80 mg QD (N=756) (PY=332.1)	Allopurinol 300/200 mg QD (N=756) (PY=337.9)
Number of Subjects with events	1	1	3
Rate (%)	0.13	0.13	0.40
95% Confidence Interval (%) +	(0.003, 0.734)	(0.003, 0.735)	(0.082, 1.155)
Fisher's exact test p-value			
Versus Allopurinol 300/200 mg QD	0.374	0.625	
Versus Febuxostat 40 mg QD		>0.999	
Relative Risk (95% CI) $			
Versus Allopurinol 300/200 mg QD	0.33 (0.03, 3.19)	0.33 (0.03, 3.20)	
Versus Febuxostat 80 mg QD	1.00 (0.06, 15.94)		
Rate per 100 patient-years	0.29	0.30	0.89
95% Confidence Interval @	(0.007, 1.622)	(0.008, 1.678)	(0.183, 2.594)

& Distributed as: allopurinol 200 mg (N=145) plus allopurinol 300 mg (N=611).
$ Continuity correction of 0.5 was used if either treatment group had 0 death events.
+ Exact confidence interval based on Binomial Distribution.
@ Exact confidence interval based on Poisson Distribution.
In column headings, N = number of subjects dosed; PY = total patient-years of exposure.

Source: Clinical Study Report, F-GT06-153, p. 230

Table 16 presents data for mortality rates in Study F-153 and aggregate data from all randomized and long-term extension studies. In the earlier studies the rate of all cause mortality was higher in febuxostat-treated subjects than in allopurinol-treated subjects. In the phase 3 RCTS, there had been 4 deaths in the febuxostat arm (rate of 0.6%) compared with 0 deaths in the allopurinol arm (see Table 2). In Study F-153, mortality is higher in the allopurinol arm (see Table 15 above). When the data from Study F-153 and the previous Phase 3 trials are combined the mortality rates in the febuxostat and the allopurinol arms are similar (0.22% vs. 0.23%).

In the-long term extension studies, the mortality rate with febuxostat is updated by an additional 500 patient-years. Two additional deaths were reported yet the mortality rate (0.38/100 pt-yrs) remains unchanged.

Table 16: All-Cause Mortality in Febuxostat Clinical Program

Treatment	N or PY	Number of Deaths	Mortality Rate	95% Confidence Interval[a]
Study F-GT06-153				
Febuxostat Total	1513	2	0.13%	0.016 - 0.477
Allopurinol	756	3	0.40%	0.082 - 1.155
Phase 3 Randomized-Controlled Studies[b]				
Febuxostat Total	2690	6	0.22%	0.082 - 0.485
Allopurinol	1277	3	0.23%	0.048 - 0.685
Long-Term Extension Studies				
Febuxostat Total	2660.9 PY	10	0.38/100 PY	0.180 - 0.691
Allopurinol	172.2 PY	0	0/100 PY	0.00 - 2.14

PY = patient year

a The 95% confidence intervals are calculated based on binomial distribution for Study F-GT06-153 and the combined Phase 3 RCT studies, and based on Poisson distribution for the long-term extension studies.

b Combined Phase 3 studies included C02-009, C02-010, and F-GT06-153.

Source: Integrated Summary of Safety; July 2008, p. 93.

2. Cardiovascular Mortality

In the previous RCTs the rate of cardiovascular mortality in febuxostat-treated patients was higher than in patients treated with allopurinol. Table **17** compares cardiovascular mortality in the previous and new RCTs. No cardiovascular deaths were seen in febuxostat-treated patients in study 153 compared to 2 cardiovascular deaths among allopurinol-treated patients. Thus, the cardiovascular mortality was not higher in the febuxostat arm, in contrast to what was observed previously.

Table 17: Cardiovascular Mortality: Previous RCTS compared with F-GT06-153*

	Febuxostat-treated patients	Allopurinol-treated patients
Previous RCTs**		
N	1177	521
Number/% with CV Mortality by MedDRA preferred term	3/ .3%	0
F-GT06-153		
N	1513	755
Number/% with CV Mortality by MedDRA preferred term	0	2/ .3%
** C0-009 and C0-010; Cross-reference tables 8 and 18.		

3. Investigator-reported primary and secondary APTC events

To assess the cardiovascular safety of febuxostat, pertinent adverse events were identified by two different categorization schemes: investigator reported APTC events based on MedDRA Preferred Term (see Table 1) and adjudicated APTC events. As described previously, investigator-reported events were identified by mapping MedDRA Preferred Terms onto certain more general categories. Primary APTC events include cardiovascular death, non-fatal MI, non-fatal stroke and non-fatal cardiac arrest. Secondary APTC events include angina, revascularization, TIA, venous and peripheral arterial vascular thrombotic events, and non-fatal congestive heart failure.

Table 18 summarizes investigator-reported primary and secondary APTC events. There are 0, 1 and 3 subjects who experienced primary APTC events in the febuxostat 40-mg, febuxostat 80-mg, and allopurinol 200/300-mg arms, respectively; this corresponds to 0, 0.1 and 0.4% of subjects experiencing events. For the combined febuxostat arms the proportion experiencing an event is 0.06%. Regarding secondary investigator-reported APTC events, proportions are similar in the three study arms. In summary, the incidence of primary and secondary investigator-reported APTC events was not increased in the febuxostat arms compared to allopurinol.

Table 18: Analysis of Primary and Secondary Investigator-Reported APTC Adverse Events (F-GT06-153)

Variable	Treatment Group n (%)		
	Febuxostat 40 mg QD (N=757)	Febuxostat 80 mg QD (N=756)	Allopurinol 300/200 mg QD (N=756)
Total Subjects With at Least One Primary or Secondary Investigator-Reported APTC Event	7 (0.92)	4 (0.53)	9 (1.19)
Primary Investigator-Reported APTC Events			
Number of subjects with events	0	1	3
Rate (%)	0.00	0.13	0.40
95% Confidence Interval (%)[a]	(0.000, 0.486)	(0.003, 0.735)	(0.082, 1.155)
Fisher's exact test p-value			
Versus Allopurinol 300/200 mg QD	0.125	0.625	
Versus Febuxostat 40 mg QD		0.500	
Relative Risk (95% CI)[b]			
Versus Allopurinol 300/200 mg QD	0.14 (0.01, 2.76)	0.33 (0.03, 3.20)	
Versus Febuxostat 40 mg QD		3.00 (0.12, 73.63)	
Primary Investigator-Reported APTC Events by Criterion			
Cardiovascular death	0	0	2 (0.26)
Nonfatal myocardial infarction	0	1 (0.13)	1 (0.13)
Nonfatal stroke	0	0	0
Nonfatal cardiac arrest	0	0	0
Secondary Investigator-Reported APTC Events			
Number of subjects with events	7	3	6
Rate (%)	0.92	0.40	0.79
95% Confidence Interval (%)[a]	(0.373, 1.896)	(0.082, 1.155)	(0.292, 1.719)
Fisher's exact test p-value			
Versus Allopurinol 300/200 mg QD	>0.999	0.507	
Versus Febuxostat 40 mg QD		0.342	
Relative Risk (95% CI)[b]			
Versus Allopurinol 300/200 mg QD	1.17 (0.39, 3.45)	0.50 (0.13, 1.99)	
Versus Febuxostat 40 mg QD		0.43 (0.11, 1.65)	
Secondary Investigator-Reported APTC Events by Criterion			
Angina	2 (0.26)	1 (0.13)	0
Coronary revascularization	2 (0.26)	0	3 (0.40)
Transient ischemic attack	1 (0.13)	1 (0.13)	1 (0.13)
Venous or arterial vascular thrombotic events	0	1 (0.13)	1 (0.13)
Nonfatal congestive heart failure	3 (0.40)	0	2 (0.26)

N = number of subjects dosed; QD = once daily.
a Exact confidence interval based on Binomial Distribution.
b Continuity correction of 0.5 was used if either treatment group had zero APTC events.
Source: Clinical Study Report, F-GT06-153, p. 167.

Table 19 presents the primary and secondary APTC event rates in long-term extension studies. The data available in the second cycle (labeled 2006) are presented alongside the data incorporating additional patient exposure since that time (labeled 2008). The data indicate that for primary APTC events the rates are somewhat lower with 2008 data compared to earlier data (1.4 vs. 1.2 events/100 patient-years for the febuxostat group). However, the event rates for febuxostat continue to be higher than for allopurinol (1.2 vs. 0.6 events /100 patient-years). Secondary APTC events were not increased in the febuxostat group previously and this continues to be the case with the updated (2008) data. Both the number and patient-years of exposure to allopurinol continue to be disproportionately low in the LTES.

Table 19: Investigator-Reported APTC Events in Long Term Studies

Investigator-Reported Primary and Secondary APTC events in Long Term Extension Studies *						
	Primary APTC Events					
	Febuxostat 80 mg		*Febuxostat - total*		*Allopurinol 300/100*	
	2006	2008	2006	2008	2006	2008
N	910	917	1143	1143	178	178
Patient years	1265	1746	1934	2661	133	172
# of subjects	*18*	*21*	*28*	*31*	*1*	*1*
Rate /100 patient years	1.4	1.2	1.45	1.2	0.75	0.6
95% CI	0.96-2.1	0.75-1.8	0.96-2.1	0.78-2.65	0.02-4.2	0.02-3.2
	Secondary APTC Events					
# of subjects	24	34	36	50	3	6
Rate/100 patient years	1.9	1.95	1.9	1.9	2.25	3.5
95% CI	1.2-2.8	1.3-2.7	1.3-2.6	1.4-2.5	0.5-6.6	1.3-7.6
*Studies include TMX-01-005 and C02-021 Source: Tables 3.6.1.2 and 3.6.1.3, 2008 NDA Amendment						

4. Adjudicated APTC Events

The design of Study F-153 specified a process to adjudicate cardiovascular adverse events using APTC criteria. A committee of 3 individuals (two cardiologists and a neurologist) adjudicated, in a blinded fashion, 319 events. As seen in Table 20, adjudicated APTC events in the new RCT (F-153) were equivalent in the allopurinol and the febuxostat 80 mg arms – 3 in each arm -- while there were no events in the febuxostat 40-mg arm.

Table 20: Analysis of Adjudicated APTC Cardiovascular Adverse Events (F-GT06-153)

Variable	Treatment Group n (%)		
	Febuxostat 40 mg QD (N=757)	Febuxostat 80 mg QD (N=756)	Allopurinol 300/200 mg QD (N=756)
All APTC Events			
Number of subjects with events	0	3	3
Rate (%)	0.00	0.40	0.40
95% Confidence Interval (%)[a]	(0.000, 0.486)	(0.082, 1.155)	(0.082, 1.155)
Fisher's exact test p-value			
Versus Allopurinol 300/200 mg QD	0.125	>0.999	
Versus Febuxostat 40 mg QD		0.125	
Relative Risk (95% CI)[b]			
Versus Allopurinol 300/200 mg QD	0.14 (0.01, 2.76)	1.00 (0.20, 4.94)	
Versus Febuxostat 80 mg QD	0.14 (0.01, 2.76)		
APTC Events Summarized by Criterion			
Cardiovascular Death	0	0	2 (0.26)
Nonfatal Myocardial Infarction	0	1 (0.13)	1 (0.13)
Nonfatal Stroke	0	2 (0.26)	0

CI=confidence interval; N=number of subjects dosed; QD=once daily.
a Exact confidence interval based on Binomial Distribution.
b Continuity correction of 0.5 was used if either treatment group had zero APTC events.
Source: Clinical Study Report, F-GT06-153, p. 168.

The Division's review of the cardiovascular events in Study F-153 identified one fatal adverse event that was adjudicated as non-cardiovascular that may have been misclassified. The subject was part of the febuxostat 40-mg arm and received a number of fire ant stings earlier in the day while at work; he subsequently died in his sleep. The review division and an Agency Cardiorenal consult concurred that this case was more accurately categorized as a sudden or unexplained death which is cardiovascular in nature. If this case is reclassified as an APTC event then the number of APTC events would be 1, 3, and 3 in the febuxostat 40-mg, 80-mg and allopurinol arms, respectively. With the reclassification, the incidence of APTC events is 0.3% in the combined febuxostat arms vs. 0.4% in the allopurinol arm. Thus, the overall incidence of cardiovascular APTC events was not increased in febuxostat-treated patients compared with allopurinol-treated patients in Study F-153.

Table 21 summarizes the data for adjudicated APTC events in the long-term extension studies updated through 2008. The number and rate of events for febuxostat-treated subjects exceeds that for allopurinol. However, examination of the individual rates by study arm provides no evidence for a dose-dependent increase in cardiovascular risk for febuxostat. Although the rate of APTC events is higher with febuxostat than with allopurinol, it is not possible to reach definitive conclusions about the risk because of the small number of events as well as the limited exposure to allopurinol in the LTES.

Table 21: Adjudicated APTC Events in the Long-Term Extension Studies by PY of Exposure

APTC Criterion	Treatment Group				
	Febuxostat				Allopurinol
	Total (N=1143) (PY=2660.9)	40 mg QD (N=12) (PY=37.7)	80 mg QD (N=917) (PY=1745.6)	120 mg QD (N=524) (PY=877.7)	All Doses (N=178) (PY=172.2)
All APTC Events					
Number of Subjects	27	1	17	9	1
Rate per 100 PY	1.01	2.66	0.97	1.03	0.58
95% CI[a]	0.669-1.476	0.067-14.793	0.567-1.559	0.469-1.947	0.015-3.235
Cardiovascular Death					
Number of Subjects	7[b]	0	4[b]	3	0
Rate per 100 PY	0.26	0.00	0.23	0.34	0.00
95% CI[a]	0.106-0.542	0-9.794	0.062-0.587	0.070-0.999	0-2.142
Nonfatal Myocardial Infarction					
Number of Subjects	11	0	8	3	1
Rate per 100 PY	0.41	0.00	0.46	0.34	0.58
95% CI[a]	0.206-0.740	0-9.794	0.198-0.903	0.070-0.999	0.015-3.235
Nonfatal Stroke					
Number of Subjects	9	1	5	3	0
Rate per 100 PY	0.34	2.66	0.29	0.34	0.00
95% CI[a]	0.155-0.642	0.067-14.793	0.093-0.668	0.070-0.999	0.000-2.142

Note: Studies included TMX-01-005 and C02-021.
APTC=Antiplatelet Trialists' Collaboration; CI=confidence interval; PY=patient-years of exposure.
a The confidence intervals are calculated based on Poisson distribution.
b Two of the three additional cardiovascular deaths were reported in the supplement to the safety update 2006
Source: Integrated Summary of Safety, July, 2008, p. 182.

As part of the adjudication process, the cardiovascular endpoints committee divided events into APTC events and non-APTC events (as well as events that were non-cardiovascular). Non-APTC events included unstable angina, coronary revascularization, TIA, cerebral revascularization, venous and peripheral arterial vascular thrombotic events, congestive heart failure, arrhythmia and other non-APTC events. Table 22 provides information about adjudicated non-APTC events in the new RCT Study F-153. While the number (and rate) of events is somewhat higher for febuxostat-treated patients compared with allopurinol-treated patients the rates are overall similar and do not demonstrate any dose-dependent increases with febuxostat.

Table 22: Analysis of Adjudicated Non-APTC Cardiovascular Events (F-GT06-153)

Variable	Treatment Group n (%)		
	Febuxostat 40 mg QD (N=757)	Febuxostat 80 mg QD (N=756)	Allopurinol 300/200 mg QD (N=756)
All Non-APTC Events			
Number of subjects with events	10	9	7
Rate (%)	1.32	1.19	0.93
95% Confidence Interval (%)[a]	(0.635, 2.416)	(0.546, 2.248)	(0.373, 1.898)
Fisher's exact test p-value			
Versus Allopurinol 300/200 mg QD	0.627	0.803	
Versus Febuxostat 40 mg QD		>0.999	
Relative Risk (95% CI)[b]			
Versus Allopurinol 300/200 mg QD	1.43 (0.55, 3.73)	1.29 (0.48, 3.43)	
Versus Febuxostat 80 mg QD	1.11 (0.45, 2.72)		
Non-APTC Events by Criterion[c]			
Angina	2 (0.26)	0	0
Coronary Revascularization	1 (0.13)	0	1 (0.13)
Transient Ischemic Attack	1 (0.13)	0	1 (0.13)
Cerebral Revascularization	0	0	0
Venous and Peripheral Arterial Vascular Thrombotic Event	0	2 (0.26)	0
Congestive Heart Failure	2 (0.26)	0	1 (0.13)
Arrhythmia, No Evidence of Ischemia	3 (0.40)	4 (0.53)	1 (0.13)
Other Non-APTC CV events	1 (0.13)	3 (0.40)	3 (0.40)

N = number of subjects dosed; QD = once daily.
a Exact confidence interval based on Binomial Distribution.
b Continuity correction of 0.5 was used if either treatment group had zero APTC events.
c Subjects with multiple events are counted only once, keeping the most severe APTC criteria
Source: Clinical Study Report, F-GT06-153, p. 172.

5. Impact of Comorbid Conditions on Risk

a. Cardiovascular Disease

With regard to cardiovascular disease there are well-established risk factors that place patients at higher risk for cardiovascular events. Cardiovascular risk factors are common in the gout patient population; these include hypertension, diabetes, renal impairment, metabolic syndrome and prior cardiovascular history. We performed a post hoc subgroup analysis to explore the rate of cardiovascular events in the febuxostat clinical trials. It is important to note that the information collected on cardiovascular risk factors was somewhat different in the different trials so the definition of cardiovascular history is not identical for the three trials (Table 23).

Table 23: Definition of Cardiovascular History in Clinical Trials

Criteria Used to Identify Patients with Cardiovascular History in Clinical Trials
For Study F-GT06-153, cardiovascular history included patients with a history of myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass graft procedure, coronary artery disease, cerebrovascular accident, transient ischemic attack/reversible ischemic neurological deficit, peripheral vascular disease, cardiac arrhythmia, venous thrombotic events, valvular heart disease, congestive heart failure, and hypertension.
For Study C02-009, cardiovascular history included patients with a history of angina, myocardial infarction, congestive heart failure, hypertension, peripheral vascular disease, and cardiac arrhythmia
For Study C02-010, cardiovascular history included patients with a history of angina, myocardial infarction, congestive heart failure, hypertension, cardiac arrhythmia, peripheral vascular disease (arterial), peripheral vascular disease (venous), congenital heart disease, syncope, and valvular heart disease.

Source: Response to FDA Information Request of 25 August 2008.

As shown in Table 24 there was a trend toward a higher frequency of APTC events in patients with a cardiovascular history both in febuxostat-treated patients and in the allopurinol controls. Consistent with the higher overall rate of APTC events with febuxostat in the previous trials, APTC events were more frequent among patients with a cardiovascular history in the febuxostat group than in controls. However, in the new study, F-153, APTC events were not more frequent in febuxostat-treated patients with a cardiovascular history than in allopurinol-treated patients with a similar history.

Table 24: Subgroup Analysis of Adjudicated APTC Events by Cardiovascular History* in Randomized Controlled Trials

	Febuxostat – all groups		Allopurinol	
CV history *	**Y**	**N**	**Y**	**N**
FGT06-153: N	***861***	***652***	**436**	***320***
Adjudicated APTC events: n (%)	3 (0.35)	0	2 (0.5)	1 (0.3)
Investigator reported primary APTC events: n (%)	1 (0.1)	0	2 (0.5)	1 (0.3)
C02-009: N	***353***	***317***	***133***	***135***
Adjudicated APTC events: n (%)	1 (0.3)	1 (0.3)	0	0
Investigator reported primary APTC events: n (%)	1 (0.3)	1 (0.3)	0	0
C02-010: N	***238***	***269***	***119***	***134***
Adjudicated APTC events: n (%)	4 (1.7)	1 (0.4)	1 (0.8)	0
Investigator reported primary APTC events: n (%)	5 (2.1)	2 (0.7)	1 (0.8)	0

*See Table 23 for criteria defining cardiovascular history in each RCT
Source: Response to FDA Information Request of 25 August 2008.

b. Renal Disease

Chronic renal impairment is a recognized risk factor for cardiovascular events. We performed a subgroup analysis of APTC events by history of renal impairment. As shown in Table 25 there was a trend to more APTC events in patients with renal impairment than in patients with normal renal function. Again, consistent with the higher overall incidence of APTC events with febuxostat in previous trials, APTC events were more frequent in the febuxostat group than the allopurinol group among patients with renal impairment in studies C0-009 and C0-010. In Study F-153, however, APTC events were not seen more commonly in patients with mild or moderate renal impairment who were taking febuxostat compared to allopurinol.

Table 25: APTC Events and Renal History in Phase 3 RCTs

	Febuxostat - all groups			Allopurinol		
Renal disease*	**normal**	**mild**	**moderate**	**normal**	**mild**	**Moderate**
FGt06-153	***531***	***716***	***266***	***255***	***365***	***136***
Adjudicated APTC events: n (%)	1 (0.2)	1 (0.1)	1 (0.4)	0	1 (0.3)	2 (1.5)
Investigator reported primary APTC events: n (%)	1 (0.2)	0	0	0	1 (0.3)	2 (1.5)
C02-009: N	***342***	***231***	***97***	***132***	***96***	***40***
Adjudicated APTC events: n (%)	0	1 (0.4)	1 (1.0)	0	0	0
Investigator reported primary APTC events: n (%)	0	1 (0.4)	1 (1.0)	0	0	0
C02-010: N	***244***	***198***	***65***	***127***	***97***	***29***
Adjudicated APTC events: n (%)	0	2 (1.0)	3 (4.6)	0	1 (1.0)	0
Investigator reported primary APTC events: n (%)	0	4 (2.0)	3 (4.6)	0	1 (1.0)	0

*based upon creatinine clearance: normal (≥ 90 mL/min), mild (60-89 mL/min), moderate (30-59 mL/min)
Source: Response to FDA Information Request of 25 August 2008.

A pharmacokinetic study was conducted in subjects with renal impairment (Study TMX-01-008). Following administration of 80 mg oral doses of febuxostat daily for 7 days, mean unbound AUC_{24} ($AUC_{24,u}$) on day 7 of febuxostat increased by about 60% in subjects with mild, moderate or severe renal impairment compared to subjects with normal renal function. Pharmacokinetics 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.

6. Relative Risk of Cardiovascular Adverse Events with Febuxostat compared with Allopurinol

In order to further explore the cardiovascular risk of febuxostat we examined the relative risk of cardiovascular adverse events in patients treated with febuxostat and allopurinol in the three pivotal randomized trials. In this type of analysis a relative risk of 1.0 indicates no increased risk compared to allopurinol. Values above 1.0 indicate an increased risk

while values below 1.0 indicate a reduced risk, compared to allopurinol. As shown in Table 26 the relative risk of adjudicated APTC events among febuxostat-treated patients in the earlier RCTs (CO2-009 and C02-010) was between 2 and 3 for different doses of febuxostat. In study F-153, the relative risk for the 40 mg and 80 mg doses of febuxostat was 0.1 and 1.0, respectively. Combining all three Phase 3 trials the relative risk for febuxostat was 1.19 compared to allopurinol. It should be noted that the upper limit of the 95 % confidence interval was 3.8, the lower limit was 0.4 and the confidence interval included 1.0. This indicates that it is not possible to exclude either a greater or a lower risk with febuxostat with much confidence.

Table 26: Relative Risk (RR) with 95% Confidence Intervals (CI) for Adjudicated APTC Events

	F-40	F-80	F-120	F-240	Total: Febuxostat treated
N	757	1279	520	134	2690
C02-009					
RR		3.01	2.99	2.00	2.00
CI		(0.1, 73.6)	(0.1,73.1)	(0.04, 100.1)	(0.1, 41.6)
C02-010					
RR		2.96	2.02		2.5
CI		(0.3, 28.3)	(0.2, 2.1)		(0.3, 21.2)
F-GTO6-153					
RR	0.1	1			0.5
CI	(0.01, 2.76)	(0.2, 4.9)			(0.1, 2.5)
All Phase 3					
RR	0.2	1.75	1.8	1.06	1.19
CI	(0, 3.5)	(0.5, 5.95)	(0.4, 8.2)	(0.1, 19.5)	(0.4, 3.8)

Source: Response to FDA Information Request of 25 August 2008

7. Cardio-renal Consult

The Agency review division consulted the Division of Cardiovascular and Renal Products (Cardiorenal division) to provide their assessment of whether the pattern of cardiovascular events indicated an increased cardiovascular risk with febuxostat. The Cardiorenal consultants examined all potential cardiovascular events in study F-153. They did not see a pattern to suggest an increased cardiovascular risk. They noted that their analysis was similar to the Applicant's analysis. They concluded that the Applicant's analysis does not suggest greater rates of cardiovascular events with febuxostat than with allopurinol. They did not recommend that further studies of cardiovascular risk with febuxostat be undertaken.

8. Other Safety Issues

Cardiovascular safety was the single clinical issue identified in previous cycles as a reason to withhold approval of febuxostat. No other clinical concerns were identified as reasons for denying approval. Nevertheless, this section will look, summarily, at other potential safety signals to ascertain that no new signals have emerged since the previous review. The method here will be, primarily, to examine the patterns of adverse events (AEs) described in the updated, Integrated Summary of Safety.

Table 27: Most Frequently Reported (≥5% in Any Treatment Group) Treatment–Emergent Adverse Events in Study F-GT06-153

	Treatment Group: n (%)		
MedDRA High Level Term Preferred Term	**Febuxostat 40 mg QD** N=757	**Febuxostat 80 mg QD** N=756	**Allopurinol All Doses** N=756
Total Subjects With at Least One AE	**429 (56.7)**	**410 (54.2)**	**433 (57.3)**
Upper Respiratory Tract Infections	**71 (9.4)**	**53 (7.0)**	**57 (7.5)**
Laryngitis	0	1 (0.1)	0
Nasopharyngitis	21 (2.8)	17 (2.2)	18 (2.4)
Pharyngitis	3 (0.4)	1 (0.1)	3 (0.4)
Rhinitis	3 (0.4)	1 (0.1)	1 (0.1)
Sinobronchitis	1 (0.1)	0	0
Sinusitis	15 (2.0)	10 (1.3)	10 (1.3)
Upper Respiratory Tract Infection	30 (4.0)	25 (3.3)	27 (3.6)
Liver Function Analyses	**63 (8.3)**	**52 (6.9)**	**50 (6.6)**
Alanine Aminotransferase Abnormal	1 (0.1)	1 (0.1)	1 (0.1)
Alanine Aminotransferase Increased	26 (3.4)	17 (2.2)	15 (2.0)
Aspartate Aminotransferase Abnormal	1 (0.1)	0	0
Aspartate Aminotransferase Increased	18 (2.4)	9 (1.2)	15 (2.0)
Blood Bilirubin Increased	1 (0.1)	2 (0.3)	3 (0.4)
Hepatic Enzyme Increased	23 (3.0)	16 (2.1)	17 (2.2)
Liver Function Test Abnormal	13 (1.7)	14 (1.9)	11 (1.5)
Transaminases Increased	2 (0.3)	3 (0.4)	1 (0.1)
Diarrhoea (Excl Infective)	**45 (5.9)**	**47 (6.2)**	**57 (7.5)**
Diarrhoea	45 (5.9)	47 (6.2)	57 (7.5)
Musculoskeletal and Connective Tissue Signs and Symptoms NEC	**43 (5.7)**	**38 (5.0)**	**32 (4.2)**
Back Pain	21 (2.8)	14 (1.9)	7 (0.9)
Flank Pain	1 (0.1)	2 (0.3)	2 (0.3)
Musculoskeletal Chest Pain	3 (0.4)	1 (0.1)	1 (0.1)
Musculoskeletal Pain	3 (0.4)	7 (0.9)	4 (0.5)
Musculoskeletal Stiffness	1 (0.1)	1 (0.1)	2 (0.3)
Neck Pain	2 (0.3)	2 (0.3)	0
Nodule on Extremity	1 (0.1)	0	0
Pain In Extremity	15 (2.0)	13 (1.7)	17 (2.2)

Note: Subjects with 1 or more AE within a level of the MedDRA term are counted only once in that level.

Excl = excluding, Incl =including, NEC= not elsewhere classified.

Source ISS p. 82

Table 28: Most Frequently Reported (≥ 5% of Subjects in the Febuxostat 40-mg QD, Febuxostat 80-mg QD or Allopurinol Group) Treatment-Emergent Adverse Events in Combined Phase 3 Randomized-Controlled Studies

	Treatment Group: n (%)		
	Febuxostat		Allopurinol
MedDRA High Level Term MedDRA Preferred Terms	**40 mg QD** (N=757)	**80 mg QD** (N=1279)	**All Doses** (N=1277)
Total Subjects with at Least 1 Adverse Event	**429 (56.7)**[*†]	**797 (62.3)**[*]	**848 (66.4)**
Upper Respiratory Tract Infections	**71 (9.4)**[*†]	**169 (13.2)**	**182 (14.3)**
Acute Sinusitis	0	0	1 (<0.1)
Acute Tonsillitis	0	1 (<0.1)	0
Laryngitis	0	3 (0.2)	0
Nasopharyngitis	21 (2.8)	73 (5.7)	61 (4.8)
Pharyngitis	3 (0.4)	7 (0.5)	6 (0.5)
Rhinitis	3 (0.4)	3 (0.2)	3 (0.2)
Sinobronchitis	1 (0.1)	0	0
Sinusitis	15 (2.0)	26 (2.0)	27 (2.1)
Upper Respiratory Tract Infection	30 (4.0)	73 (5.7)	96 (7.5)
Musculoskeletal and Connective Tissue Signs and Symptoms NEC	**43 (5.7)**	**99 (7.7)**	**99 (7.8)**
Back Pain	21 (2.8)	38 (3.0)	31 (2.4)
Chest Wall Pain	0	0	0
Flank Pain	1 (0.1)	3 (0.2)	5 (0.4)
Musculoskeletal Chest Pain	3 (0.4)	5 (0.4)	2 (0.2)
Musculoskeletal Pain	3 (0.4)	17 (1.3)	8 (0.6)
Musculoskeletal Stiffness	1 (0.1)	4 (0.3)	9 (0.7)
Neck Pain	2 (0.3)	5 (0.4)	5 (0.4)
Nodule on Extremity	1 (0.1)	1 (<0.1)	0
Pain in Extremity	15 (2.0)	40 (3.1)	48 (3.8)
Shoulder Pain	0	0	0
Joint Related Signs and Symptoms	**31 (4.1)**[†]	**81 (6.3)**	**77 (6.0)**
Arthralgia	26 (3.4)	73 (5.7)	65 (5.1)
Joint Crepitation	1 (0.1)	1 (<0.1)	0
Joint Effusion	1 (0.1)	3 (0.2)	3 (0.2)
Joint Range of Motion Decreased	1 (0.1)	2 (0.2)	1 (<0.1)
Joint Stiffness	2 (0.3)	4 (0.3)	4 (0.3)
Joint Swelling	2 (0.3)	4 (0.3)	6 (0.5)
Diarrhoea (Excl Infective)	**45 (5.9)**	**94 (7.3)**	**91 (7.1)**
Diarrhoea	45 (5.9)	94 (7.3)	91 (7.1)

Note: Phase 3 studies included C02-009, C02-010, and F-GT06-153.
NEC = not elsewhere classified.
* Indicates statistically significant difference versus allopurinol ($p \leq 0.05$).
† Indicates statistically significant difference versus febuxostat 80 mg QD ($p \leq 0.05$).
Source ISS p. 84

Table 29: Continuation of Table 28.

MedDRA High Level Term MedDRA Preferred Terms	Treatment Group: n (%) Febuxostat 40 mg QD (N=757)	 80 mg QD (N=1279)	 Allopurinol All Doses (N=1277)
Liver Function Analyses	**63 (8.3)**	**82 (6.4)**	**77 (6.0)**
Alanine Aminotransferase Abnormal	1 (0.1)	1 (<0.1)	1 (<0.1)
Alanine Aminotransferase Increased	26 (3.4)	27 (2.1)	21 (1.6)
Aspartate Aminotransferase Abnormal	1 (0.1)	0	0
Aspartate Aminotransferase Increased	18 (2.4)	17 (1.3)	20 (1.6)
Blood Bilirubin Increased	1 (0.1)	3 (0.2)	4 (0.3)
Hepatic Enzyme Abnormal	0	1 (<0.1)	0
Hepatic Enzyme Increased	23 (3.0)	25 (2.0)	30 (2.3)
Liver Function Test Abnormal	13 (1.7)	23 (1.8)	19 (1.5)
Transaminases Increased	2 (0.3)	3 (0.2)	1 (<0.1)
Headaches NEC	**21 (2.8)***	**53 (4.1)**	**62 (4.9)**
Cluster Headache	0	1 (<0.1)	0
Headache	21 (2.8)	51 (4.0)	57 (4.5)
Sinus Headache	0	2 (0.2)	4 (0.3)
Tension Headache	0	0	3 (0.2)
Nausea and Vomiting Symptoms	**22 (2.9)**	**47 (3.7)***	**28 (2.2)**
Nausea	20 (2.6)	39 (3.0)	21 (1.6)
Vomiting	5 (0.7)	16 (1.3)	13 (1.0)

Note: Phase 3 studies included C02-009, C02-010, and F-GT06-153.
NEC = not elsewhere classified.
* Indicates statistically significant difference versus allopurinol ($p \leq 0.05$).
† Indicates statistically significant difference versus febuxostat 80 mg QD ($p \leq 0.05$).

ISS p. 85

Table 27 and Table 28 summarize AEs for Study F-153 and for all Phase 3 RCTs, respectively. In Study F-153 (Table 27) the proportion of subjects experiencing at least one AE was approximately the same in all three groups: 57%, 54% and 57% in febuxostat 40 mg, febuxostat 80 mg and allopurinol arms, respectively. For the larger group of subjects enrolled in *all* phase 3 RCTs, who are taking the same doses of these drugs (Table 28), the comparable proportions are: 57%, 62% and 66%. That is, the percent experiencing an AE is higher in the control (allopurinol) group. Taken together, these data do not point to an overall excess of AEs among febuxostat-treated patients.

Analysis of data in individual categories reveals that, with the exception of liver function analyses, there is no category for which the event rate in *both* febuxostat arms exceeds the event rate with the allopurinol arm. That is, no other adverse event category showed a clear pattern of an increase compared to the allopurinol control.

For the category of Liver Function Analyses, data in Study F-153 show a higher proportion of subjects with abnormal liver function analyses in the febuxostat 40-mg arm (8%) than in either the febuxostat 80 mg arm or the allopurinol arm (approximately 7% for each). (In the larger group of subjects in all phase 3 RCTs the proportions for the respective arms are, approximately: 8%, 6% and 6%.) Though a higher proportion of febuxostat-treated subjects experienced abnormalities here, the absence of a dose effect makes it difficult to conclude there is a causal relationship. Moreover, consider the data in Table 30 and 31. In both tables there is no consistent pattern between drug dose and changes or abnormalities of hepatic function. Finally, it should be noted with regard to

hepatic function that no cases of acute liver failure were identified, nor were there any Hy's law cases.

In summary, while some increases in liver enzymes were seen, no evidence of new safety signals in other categories of adverse events emerged in the new study.

Table 30: Shifts Relative to Normal Range in Hepatic Laboratory Parameters in the Combined Phase 3 Randomized-controlled Studies

	Febuxostat					Allopurinol
Hepatic Parameter Shift	Placebo (N=134)	40 mg QD (N=757)	80 mg QD (N=1279)	120 mg QD (N=520)	240 mg QD (N=134)	All Doses (N=1277)
Total Bilirubin						
Shift to High	9/126 (7)	25/696 (4)	45/1174 (4)	37/490 (8)	10/122 (8)	46/1163 (4)
Shift to Low	5/128 (4)	11/704 (2)*	35/1197 (3)	17/503 (3)	3/127 (2)	43/1181 (4)
Alkaline Phosphatase						
Shift to High	5/128 (4)	16/684 (2)	44/1170 (4)	26/496 (5)	3/121 (2)	51/1171 (4)
Shift to Low	1/128 (<1)	1/709 (<1)	8/1200 (<1)	2/503 (<1)	0/126	4/1190 (<1)
AST						
Shift to High	32/119 (27)	186/629 (30)	332/1030 (32)	156/437 (36)	35/113 (31)	333/1079 (31)
Shift to Low	0/129	1/705 (<1)	5/1201 (<1)	3/506 (<1)	0/127	4/1197 (<1)
ALT						
Shift to High	38/107 (36)	198/578 (34)	349/947 (37)	152/395 (38)	38/110 (35)	354/974 (36)
Shift to Low	0/129	0/710	1/1204 (<1)	1/506 (<1)	0/127	0/1200

Note: Studies included C02-009, C02-010, and F-GT06-153.
* Indicates statistical significance versus allopurinol ($p \leq 0.05$).
Source ISS p. 260

Table 31: Hepatic Elevations in Combined Phase 3 Randomized-Controlled Studies

	Treatment Group: n/N (%)					
	Placebo	Febuxostat				Allopurinol
Hepatic Chemistry Parameter Elevation Criterion	N=134 n/N (%)	40 mg QD N=757 n/N (%)	80 mg QD N=1279 n/N (%)	120 mg N=520 n/N (%)	240 mg N=134 n/N (%)	100/200/ 300 mg QD N=1277 n/N (%)
ALT						
≥2×Upper Limit of Normal	8/129 (6)	70/711 (10)	135/1204 (11)*	65/506 (13)	10/127 (8)	102/1200 (9)
≥3×Upper Limit of Normal	1/129 (<1)	23/711 (3)	39/1204 (3)	24/506 (5)	3/127 (2)	23/1200 (2)
≥5×Upper Limit of Normal	0/129	3/711 (<1)	3/1204 (<1)	1/506 (<1)	2/127 (2)	6/1200 (<1)
≥10×Upper Limit of Normal	0/129	0/711	0/1204	0/506	1/127 (<1)	2/1200 (<1)
AST						
≥2×Upper Limit of Normal	7/129 (5)	46/710 (6)	69/1204 (6)	38/506 (8)	11/127 (9)	63/1200 (5)
≥3×Upper Limit of Normal	1/129 (<1)	10/710 (1)	16/1204 (1)	13/506 (3)	2/127 (2)	24/1200 (2)
≥5×Upper Limit of Normal	1/129 (<1)	3/710 (<1)	1/1204 (<1)*	2/506 (<1)	2/127 (2)	8/1200 (<1)
≥10×Upper Limit of Normal	0/129	0/710	0/1204	1/506 (<1)	0/127	3/1200 (<1)
ALT and AST Concurrently						
≥2×Upper Limit of Normal	4/129 (3)	33/710 (5)	56/1204 (5)*	28/506 (6)	6/127 (5)	36/1200 (3)
≥3×Upper Limit of Normal	0/129	8/710 (1)	10/1204 (<1)	8/506	2/127 (2)	12/1200 (1)
ALT and Total Bilirubin ≥2 mg/dL Concurrently						
≥2×Upper Limit of Normal	0/129	0/711	2/1204 (<1)	0/506	1/127 (<1)	2/1200 (<1)
≥3×Upper Limit of Normal	0/129	0/711	0/1204	0/506	1/127 (<1)	1/1200 (<1)
≥5×Upper Limit of Normal	0/129	0/711	0/1204	0/506	1/127 (<1)	1/1200 (<1)
≥10×Upper Limit of Normal	0/129	0/711	0/1204	0/506	1/127 (<1)	0/1200
AST and Total Bilirubin ≥2 mg/dL Concurrently						
≥2×Upper Limit of Normal	0/129	0/710	1/1204 (<1)	0/506	1/127 (<1)	2/1200 (<1)
≥3×Upper Limit of Normal	0/129	0/710	0/1204	0/506	1/127 (<1)	1/1200 (<1)
≥5×Upper Limit of Normal	0/129	0/710	0/1204	0/506	1/127 (<1)	1/1200 (<1)
≥10×Upper Limit of Normal	0/129	0/710	0/1204	0/506	0/127	0/1200
ALT and Alkaline Phosphatase Concurrently[a]						
≥2×Upper Limit of Normal	0/129	0/711	1/1204 (<1)	0/506	0/127	0/1200
≥3×Upper Limit of Normal	0/129	0/711	1/1204 (<1)	0/506	0/127	0/1200
≥5×Upper Limit of Normal	0/129	0/711	1/1204 (<1)	0/506	0/127	0/1200
≥10×Upper Limit of Normal	0/129	0/711	0/1204	0/506	0/127	0/1200
AST and Alkaline Phosphatase Concurrently[a]						
≥2×Upper Limit of Normal	0/129	0/710	2/1204 (<1)	0/506	0/127	0/1200
≥3×Upper Limit of Normal	0/129	0/710	0/1204	0/506	0/127	0/1200
≥5×Upper Limit of Normal	0/129	0/710	0/1204	0/506	0/127	0/1200
≥10×Upper Limit of Normal	0/129	0/710	0/1204	0/506	0/127	0/1200

Note: Studies included C02-009, C02-010, and F-GT06-153. Studies allowed subject to enroll with ALT or AST 1.5×ULN.
a Elevated alkaline phosphatase is defined as ≥2×ULN.
* Indicates statistical significance versus allopurinol ($p \leq 0.05$).

E. Conclusions: Study F- GT 06 -153

Study F-153 was conducted to assess cardiovascular risk with febuxostat because of a possible safety signal identified in earlier trials. The areas of concern in previous trials included a higher rate of all cause mortality, cardiovascular mortality, investigator-reported APTC events and adjudicated APTC events.

Study F-153 enrolled approximately 3-fold more subjects per study arm as the previous RCTs. Similar proportions of patients had risk factors for cardiovascular disease as in the previous studies, including cardiovascular history and renal impairment. Examination of the events of concern from the previous studies including all cause mortality, cardiovascular mortality, investigator-reported APTC events and adjudicated APTC events showed no definitive evidence of an increased cardiovascular risk.

VI. Deliberations of the Arthritis Advisory Committee

The Arthritis Advisory Committee (AC) met on November 24, 2008 to discuss and evaluate approval of Febuxostat. The Applicant, FDA, a cardiologist and a rheumatologist made presentations. The cardiologist, Dr. Milton Packer presented a discussion of the difficulties of evaluating trials wherein small numbers of events were present. The rheumatologist, Dr. John Cush, presented an overview of gout as a disease as well as currently available treatments and practice patterns.

The AC voted 12-0 (with 1 abstention) to approve both the 40 and 80-mg doses of febuxostat. Concerns about cardiovascular safety were articulated, but these did not affect the final decision of the committee to approve the drug. The committee's deliberations reflected the conviction that there is a need for new medication to treat gout. In part new treatments are needed because some patients are intolerant of current therapies; in part new treatments are needed because gout is treated suboptimally even when patients take currently available therapies. Regardless of the reason, AC members seemed to agree that there is a population with an unmet medical need which would benefit from febuxostat.

In light of the concerns about a cardiovascular safety signal, there seemed to be a consensus that extensive post-marketing evaluation, looking at safety, should be undertaken. Though there was extensive discussion about the need for further post-marketing evaluation, there was no consensus about the best type of study to pursue and whether or not these should be outcome or observational studies.

VII. Conclusions

Review of the data from the two Phase 3 trials at the time of the second cycle submission in 2006 suggested a cardiovascular safety signal for febuxostat based on a higher rate of mortality, mortality due to cardiovascular events and cardiovascular serious adverse events based on APTC endpoints. These findings suggested that treatment with febuxostat may be associated with a higher risk of cardiovascular events. However, the findings were generally based on small numbers of events and broad confidence intervals including values compatible with both increased and decreased risk. These factors introduced a significant element of uncertainty into the conclusions.

To address the cardiovascular risk of febuxostat the Applicant carried out an additional randomized clinical trial (Study F-153) that was designed to determine whether, in a larger study, the cardiovascular safety signal seen previously would be seen again. This trial enrolled approximately 3-fold more patients per study arm than the previous trials, providing an overall size larger than the two previous Phase 3 studies combined. Study F-153 studied 40 mg febuxostat daily in addition to the 80 mg dose in order to assess the safety and efficacy of a lower dose. The study design specified collection of information on cardiovascular-thromboembolic events and included a procedure for adjudication of potential APTC events by a blinded panel.

Study F-153 showed efficacy of febuxostat based on an increase in the proportion of patients achieving a serum urate level below 6 mg/dL for the 80 mg dose compared to the allopurinol control. Efficacy of the 40 mg dose was demonstrated based on a statistical demonstration of non-inferiority to allopurinol. For subjects with a baseline sUA $\geq$ 10 mg/dL febuxostat was generally less effective than for those with sUA < 10 mg/dL. For the prespecified subgroup of patients with mild or moderate renal impairment both febuxostat 40-mg and 80-mg doses were found statistically superior to allopurinol.

Examination of cardiovascular events in Study F-153 did not show a higher rate of cardiovascular-thromboembolic events with febuxostat than with allopurinol control. The overall mortality rate and cardiovascular mortality rate were not increased. In addition, neither the investigator-reported primary and secondary APTC events nor the adjudicated APTC events were more frequent in the febuxostat arms than in the allopurinol arm. Two post hoc subgroup analyses were carried out to assess cardiovascular events in patients with pre-existing risk factors: patients with a prior cardiac history and patients with pre-existing renal insufficiency. While there were too few events to reach firm conclusions, in neither subgroup was there a higher rate of cardiovascular events in the febuxostat-treated patients than in the allopurinol-treated patients.

The new study – Study F-153 – did not confirm the previous observation of a higher rate of cardiovascular events with febuxostat than with control. At the same time, however, there were few events, overall, in this new study. This raises a question about how conclusively the new study can exclude an increased cardiovascular risk with febuxostat.

In summary the efficacy of both the 40 mg and 80 mg doses of febuxostat is well established by the randomized clinical trial data. Though questions remain about cardiovascular safety, a cardiovascular risk with febuxostat was not demonstrated in the new study. Furthermore, while there are existing treatments for hyperuricemia on the market, there continue to be individuals who are intolerant of these treatments and who would benefit from a new drug for this indication. Thus the risk-benefit profile is favorable and suggests that febuxostat should be approved for hyperuricemia in gout.

VIII. Recommendations

A. Approval of 40 mg dose

Study F-153 demonstrates that Febuxostat, in the 40-mg dose, has similar efficacy to allopurinol for the general population with gout. This study also points to the possibility that, for those with renal impairment, the 40-mg dose of febuxostat has greater efficacy than allopurinol. No cardiovascular toxicity is seen in Study F-153 with the 40-mg dose of febuxostat.

For these reasons, the risk benefit profile for febuxostat 40 mg appears favorable and supports approval of this dose regimen.

B. Approval of 80 mg dose

All phase 3 randomized controlled trials demonstrate that febuxostat 80 mg is superior to allopurinol for the general population with hyperuricemia and gout. Over 3800 persons were involved in these trials and over 1250 were exposed to the 80 mg dose. Data from these trials reveal that over two-thirds of those receiving the 80-mg dose of febuxostat met the primary endpoint. Additionally, the 80-mg dose is statistically superior to the 40-mg dose.

For the sub-group of patients with mild or moderate renal impairment, the 80-mg dose was also superior to allopurinol as well as to the 40-mg dose of febuxostat.

For the sub-group of patients with a high baseline sUA the efficacy of febuxostat is reduced for both the 40 and 80-mg doses (see Table 13). The 40-mg dose of febuxostat results in achievement of the primary endpoint in only 27% in the group with a sUA $\geq$ 10 mg/dL, compared with over 50% in those with sUA < 10 mg/dL. In comparison, the 80-mg dose enables 49% in this group to achieve the primary endpoint. Consequently, the 80-mg dose may be needed for satisfactory treatment of gout in this population.

In the two earlier RCTs (conducted and reviewed at FDA during the first and second cycles) a possible cardiovascular safety signals was identified with the 80-mg dose of febuxostat. However, as described previously, there were limitations to the data and

these limitations introduced uncertainty about the existence and/or nature of the signal. The newer RCT (Study F-153) failed to confirm a cardiovascular safety signal.

The absence of new evidence to indicate a safety signal in the new trial, combined with the well-established efficacy, suggest a favorable risk-benefit profile and support approval of the 80-mg dose.

C. Dose initiation and reassessment

b(4)

b(4)

D. Prophylaxis

In the initial two RCTs, prophylaxis for gout flare was given during the first 8 weeks of the trials, which then continued for 28 and 52 weeks. In both trials, gout flares developed in the time period immediately after prophylaxis ended. In contrast, in Study F-153, prophylaxis continued for the entire 28 weeks of the trial. In this study, there was no evidence of a spurt of flares at any time during the study.

Since flares are most common as sUA is being reduced, prophylaxis should, optimally, begin at the same time as urate-lowering therapy; it should then continue for some period of time. Since flares did not manifest themselves to the same level when prophylaxis was continued for 6 months, this would represent a good strategy to follow. Data to describe the frequency of flares after this point are needed and could be collected in post-marketing studies.

IX. Post-Marketing Studies

A. Issues

There are specific safety issues that would mandate collection and analysis of additional data from post-marketing studies. These issues are outlined here. The next section describes the types of studies that might be undertaken.

1. Safety

Future studies should further evaluate cardiovascular safety. The major concern of the Arthritis Advisory Committee (AC) as well as FDA reviewers involved the possibility of a cardiovascular safety signal. As described previously, there is considerable uncertainty about this signal and the overall risk-benefit profile was thought to favor approval of the drug. However, it is the consensus of both the AC and reviewers at FDA that efforts be made to collect post-marketing data suitable for definitive assessment of cardiovascular risk.

Though persons with gout have significant risk factors for cardiovascular disease, the absolute rate of cardiovascular events may be low. For example, in all three RCTs close to 4000 persons were enrolled. In total, there were 14 adjudicated APTC events; that is, 0.3% of enrollees experienced an APTC-defined cardiovascular event (including cardiovascular death, non-fatal stroke and non-fatal MI). Any future study that is undertaken should be able to take these factors into consideration and be sufficiently large that a meaningful increase in risk could be identified.

2. Subgroups

Renal impairment is a common co-morbidity in patients with gout. Since febuxostat is normally excreted in urine, patients with renal impairment experience a higher exposure to the drug. In light of this higher exposure level, it is possible that patients with renal impairment may develop toxicity at a lower dose. Thus, it is important to insure that future studies include a sufficient number of patients with and without renal impairment so that adequate conclusions about the safety of febuxostat, for this subgroup, can be drawn.

Two other subgroups should also receive special attention in a post-marketing study of cardiovascular safety: women and the elderly. The trial should enroll adequate numbers of women because the safety data for febuxostat in women are limited; only 5% of enrolled patients were women. While there are a variety of reasons why relatively few women were enrolled in the Phase 3 trials a post-marketing study could enroll larger numbers of women. It would also be important to enroll adequate numbers of the elderly because cardiovascular risk increases with increasing age.

In summary, a post-marketing study should include adequate numbers of women, the elderly and patients with renal impairment to better characterize cardiovascular safety in these subgroups.

B. Nature of study: outcome vs. observational

Definitive analysis of the possible cardiovascular safety signal requires a large outcome study. Such a study would, by definition, involve a large, long-term, randomized trial. The number of enrollees, the manner of randomization and the duration of the study should be optimally defined so as to maximize the chance of identifying or excluding the presence of a cardiovascular safety signal.

The challenges of this sort of a post-marketing study cannot, though, be underestimated. A protocol needs to be designed that is both feasible and able to meet its objectives. Coordination of a large number of investigators and sites will be required. Thus the start up of such a trial may not be rapid. Additionally, recruitment of subjects could be slow: patients may be reluctant to participate in a randomized trial where they could receive the "control" rather than the new drug. Consequently, it is unlikely that results will be available in a short time frame.

Though the focus of this outcome study would be safety, it should be additionally noted that patients who have failed allopurinol (or who have been otherwise intolerant of it), would probably be excluded from enrollment. Therefore, neither the safety nor the efficacy in this group could be addressed.

Despite the challenges of an outcome study, the evidence suggesting a possible cardiovascular risk requires that we get more definitive information.

An observational study, or registry, in contrast, would lack systematic design and randomization. It may or may not include an adequate number of patients treated with allopurinol and therefore it may be difficult to draw definitive conclusions comparing the safety of febuxostat compared to alternative treatment. The benefits of an observational study include simplicity of initiation and possibly earlier availability of data. Probably the major advantage of an observational trial would be the inclusion of patients who have either failed or been intolerant of allopurinol.

In summary, there is a role for both an outcome and an observational study. The design, patient groups, and timing of each would seem to complement each other. For these

reasons, the Applicant should be required to design and carry out both a randomized cardiovascular outcome study and an observational study.

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

/s/

Jane Gilbert
12/19/2008 03:20:42 PM
MEDICAL OFFICER

Jeffrey N Siegel
12/19/2008 03:51:23 PM
MEDICAL OFFICER

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: October 14, 2008

From: Thomas A. Marciniak, M.D.
Medical Team Leader
Division of Cardiovascular and Renal Products (HFD-110)

Subject: Cardiovascular events with febuxostat, NDA 21-856

Through: Norman Stockbridge, M.D., Ph.D.
Division Director

To: Matthew Sullivan
Division of Anesthesia, Analgesia and Rheumatology Products (HFD-170)

This memo responds to your consult to us dated August 14, 2008, requesting our responses to specific questions regarding cardiovascular (CV) events analyzed in a complete response for febuxostat, a xanthine oxidase inhibitor for the treatment of hyperuricemia in patients with gout. You had previously consulted us in 2006 regarding thirteen CV events in the development program. Your consult request includes an excellent succinct summary of the submitted studies and regulatory responses to date. We respond to your new questions below.

Responses to Questions

1. In previous trials a possible safety signal for cardiovascular thrombotic events was noted. Are Antiplatelet Trialists' Collaboration (APTC) criteria appropriate to use to assess this risk?

We commented on the APTC criteria in our previous consult: The APTC definitions used for the original APTC meta-analysis were terms for thromboembolic and bleeding events used to provide some commonality among the many endpoints used in the studies included in the meta-analysis. The APTC group was unable to specify optimal, detailed criteria (because the supporting data were not collected prospectively), to collect more information on the cases, or even to re-adjudicate them—the APTC group was forced by practicality to accept the diagnoses used in the original studies. Hence we are unaware of strict APTC criteria that can be used to adjudicate cases from case report forms.

For the earlier analyses the sponsor had extended the APTC events to other domains such as arrhythmias (and that was not inappropriate as we commented in our earlier consult). For the

analyses of Study 153 the sponsor has restricted the events of interest to the APTC events (MI, stroke, vascular death) defined in the original 1994 BMJ paper. If you have strong evidence to justify MI, stroke, and vascular death as the only possible CV events related to febuxostat, then it would be appropriate to focus upon them. However, we believe that it is still unclear whether febuxostat has any CV toxicity and, if it does, what it is. Hence we recommend treating the febuxostat CV event analyses for Study 153 as any other NDA submission safety analyses: Classify all CV events into specific as well as more aggregated categories and judge whether there are any CV safety signals.

2. Specifically for the new trial (F- GT 06-153), were the APTC criteria applied properly? For example, patient #33392002 was a 60 year old gentleman with numerous cardiac risk factors who expired in his sleep a day after having received several ant bites while at work. This event was adjudicated as a non-APTC event; it was hypothesized that it was due to hypotension–induced myocyte ischemia resulting from an allergic reaction to fire ant stings. Was this appropriate? Similarly, of the 80 SAEs, only six were confirmed by the adjudication process as APTC events even though a number of additional events had cardiac features (see Clinical Study Report Table 43, p. 170. The table is also appended to this consult request.) Can you comment on whether these represent an accurate application of APTC criteria?

We agree that from the provided details patient #33392002 should be classified as a sudden death. Regarding other AEs, we have classified them into typical CV categories and discuss them under response 3 below.

3. Please provide your assessment of whether the overall pattern of cardiovascular events presented in the febuxostat trials suggests an increased cardiovascular risk associated with febuxostat treatment and/or warrants additional investigation? If so, in light of the limited number of gout patients available for study, please provide recommendations on how the cardiovascular risk of febuxostat might be further assessed.

We examined and classified all potential cardiovascular events in Study 153 and show our results in the Appendix. For Study 153 we do not see a pattern suggesting an increased CV risk associated with febuxostat. While in our tables angina is only reported in the febuxostat groups, the other events resulting from coronary atherosclerosis (MIs, coronary disease—usually revascularizations) are slightly more frequent in the allopurinol group. There is no consistent or even slightly suggestive differential pattern of CV events in Study 153.

With regard to a lack of a differential of CV events in Study 153 between febuxostat and the control allopurinol our results are similar to the sponsor's analyses. We did not attempt to reclassify all potential CV events in all febuxostat trials. We do note that the sponsor's analyses of the combined trial data do not suggest greater rates of CV events with febuxostat than with allopurinol. We do not recommend further studies of CV risk for febuxostat.

Reference

Antiplatelet Trialists' Collaboration (1994). "Collaborative overview of randomised trials of antiplatelet therapy Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients." BMJ 308(6921): 81-106.

Appendix: Rates of Cardiovascular Events by Treatment Arm in Study 153

Key
frequency
row percentage

Treatment	died: no	died: yes	Total
ALLOPURINOL 200 MG	143	2	145
	98.62	1.38	100.00
ALLOPURINOL 300 MG	610	1	611
	99.84	0.16	100.00
FEBUXOSTAT 40 MG	756	1	757
	99.87	0.13	100.00
FEBUXOSTAT 80 MG	755	1	756
	99.87	0.13	100.00
Total	2,264	5	2,269
	99.78	0.22	100.00

Treatment	Any CV AE: no	Any CV AE: yes	Total
ALLOPURINOL 200 MG	129	16	145
	88.97	11.03	100.00
ALLOPURINOL 300 MG	576	35	611
	94.27	5.73	100.00
FEBUXOSTAT 40 MG	712	45	757
	94.06	5.94	100.00
FEBUXOSTAT 80 MG	714	42	756
	94.44	5.56	100.00
Total	2,131	138	2,269
	93.92	6.08	100.00

Treatment	Atrial fibrillation or flutter: no	Atrial fibrillation or flutter: yes	Total
ALLOPURINOL 200 MG	144	1	145
	99.31	0.69	100.00
ALLOPURINOL 300 MG	609	2	611
	99.67	0.33	100.00
FEBUXOSTAT 40 MG	753	4	757
	99.47	0.53	100.00
FEBUXOSTAT 80 MG	752	4	756
	99.47	0.53	100.00

Total	2,258	11	2,269
	99.52	0.48	100.00

Treatment	TIA no	yes	Total
ALLOPURINOL 200 MG	145	0	145
	100.00	0.00	100.00
ALLOPURINOL 300 MG	610	1	611
	99.84	0.16	100.00
FEBUXOSTAT 40 MG	756	1	757
	99.87	0.13	100.00
FEBUXOSTAT 80 MG	755	1	756
	99.87	0.13	100.00
Total	2,266	3	2,269
	99.87	0.13	100.00

Treatment	Syncope no	yes	Total
ALLOPURINOL 200 MG	144	1	145
	99.31	0.69	100.00
ALLOPURINOL 300 MG	607	4	611
	99.35	0.65	100.00
FEBUXOSTAT 40 MG	756	1	757
	99.87	0.13	100.00
FEBUXOSTAT 80 MG	756	0	756
	100.00	0.00	100.00
Total	2,263	6	2,269
	99.74	0.26	100.00

Treatment	Stroke no	yes	Total
ALLOPURINOL 200 MG	144	1	145
	99.31	0.69	100.00
ALLOPURINOL 300 MG	611	0	611
	100.00	0.00	100.00
FEBUXOSTAT 40 MG	757	0	757
	100.00	0.00	100.00
FEBUXOSTAT 80 MG	755	1	756
	99.87	0.13	100.00
Total	2,267	2	2,269

	99.91	0.09	100.00

Treatment	Hypertension no	yes	Total
ALLOPURINOL 200 MG	140	5	145
	96.55	3.45	100.00
ALLOPURINOL 300 MG	594	17	611
	97.22	2.78	100.00
FEBUXOSTAT 40 MG	742	15	757
	98.02	1.98	100.00
FEBUXOSTAT 80 MG	740	16	756
	97.88	2.12	100.00
Total	2,216	53	2,269
	97.66	2.34	100.00

Treatment Treatment	MI/sudden death no no	yes yes	Total Total
ALLOPURINOL 200 MG	143	2	145
	98.62	1.38	100.00
ALLOPURINOL 300 MG	610	1	611
	99.84	0.16	100.00
FEBUXOSTAT 40 MG	756	1	757
	99.87	0.13	100.00
FEBUXOSTAT 80 MG	755	1	756
	99.87	0.13	100.00
Total	2,264	5	2,269
	99.78	0.22	100.00

Treatment	Coronary artery disease no	yes	Total
ALLOPURINOL 200 MG	144	1	145
	99.31	0.69	100.00
ALLOPURINOL 300 MG	609	2	611
	99.67	0.33	100.00
FEBUXOSTAT 40 MG	755	2	757
	99.74	0.26	100.00
FEBUXOSTAT 80 MG	756	0	756
	100.00	0.00	100.00
Total	2,264	5	2,269

	99.78	0.22	100.00

Treatment	Conduction block no	yes	Total
ALLOPURINOL 200 MG	145	0	145
	100.00	0.00	100.00
ALLOPURINOL 300 MG	608	3	611
	99.51	0.49	100.00
FEBUXOSTAT 40 MG	753	4	757
	99.47	0.53	100.00
FEBUXOSTAT 80 MG	753	3	756
	99.60	0.40	100.00
Total	2,259	10	2,269
	99.56	0.44	100.00

Treatment	Heart failure no	yes	Total
ALLOPURINOL 200 MG	144	1	145
	99.31	0.69	100.00
ALLOPURINOL 300 MG	610	1	611
	99.84	0.16	100.00
FEBUXOSTAT 40 MG	754	3	757
	99.60	0.40	100.00
FEBUXOSTAT 80 MG	756	0	756
	100.00	0.00	100.00
Total	2,264	5	2,269
	99.78	0.22	100.00

Treatment	Tachyarrhythmia no	yes	Total
ALLOPURINOL 200 MG	144	1	145
	99.31	0.69	100.00
ALLOPURINOL 300 MG	607	4	611
	99.35	0.65	100.00
FEBUXOSTAT 40 MG	751	6	757
	99.21	0.79	100.00
FEBUXOSTAT 80 MG	754	2	756
	99.74	0.26	100.00
Total	2,256	13	2,269
	99.43	0.57	100.00

Treatment	Bradyarrhythmia no	yes	Total
ALLOPURINOL 200 MG	144	1	145
	99.31	0.69	100.00
ALLOPURINOL 300 MG	608	3	611
	99.51	0.49	100.00
FEBUXOSTAT 40 MG	754	3	757
	99.60	0.40	100.00
FEBUXOSTAT 80 MG	752	4	756
	99.47	0.53	100.00
Total	2,258	11	2,269
	99.52	0.48	100.00

Treatment	Angina no	yes	Total
ALLOPURINOL 200 MG	145	0	145
	100.00	0.00	100.00
ALLOPURINOL 300 MG	611	0	611
	100.00	0.00	100.00
FEBUXOSTAT 40 MG	755	2	757
	99.74	0.26	100.00
FEBUXOSTAT 80 MG	755	1	756
	99.87	0.13	100.00
Total	2,266	3	2,269
	99.87	0.13	100.00

Treatment	Migraine no	yes	Total
ALLOPURINOL 200 MG	145	0	145
	100.00	0.00	100.00
ALLOPURINOL 300 MG	610	1	611
	99.84	0.16	100.00
FEBUXOSTAT 40 MG	756	1	757
	99.87	0.13	100.00
FEBUXOSTAT 80 MG	755	1	756
	99.87	0.13	100.00
Total	2,266	3	2,269
	99.87	0.13	100.00

Treatment	Hypotension no	yes	Total
ALLOPURINOL 200 MG	143	2	145
	98.62	1.38	100.00
ALLOPURINOL 300 MG	611	0	611
	100.00	0.00	100.00
FEBUXOSTAT 40 MG	757	0	757
	100.00	0.00	100.00
FEBUXOSTAT 80 MG	754	2	756
	99.74	0.26	100.00
Total	2,265	4	2,269

Appears This Way
On Original

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

/s/

Thomas Marciniak
10/14/2008 09:39:33 AM
MEDICAL OFFICER

Norman Stockbridge
10/14/2008 09:45:48 AM
MEDICAL OFFICER

DIVISION DIRECTOR SUMMARY REVIEW AND BASIS FOR APPROVABLE ACTION

DATE:	July 31, 2006
DRUG:	Uloric (febuxostat, 80-mg and 120-mg tablets)
NDA:	21-856
NDA Code:	Type 1S NDA
SPONSOR:	TAP Pharmaceutical Products, Inc.
INDICATION:	For the management of hyperuricemia in patients with gout

TAP Pharmaceutical Products submitted NDA 21-856 in support of marketing approval for Uloric, (febuxostat, 80-mg and 120-mg tablets), on December 15, 2004. An approvable letter was issued on October 14, 2005. The letter noted the following concerns and required responses to those concerns before the application could be approved:

1. Due to the finding that exposure to Uloric appeared to increase the risk of cardiac thromboembolic events compared to placebo or allopurinol, the sponsor was asked to either provide further comparative controlled clinical safety data or to reanalyze the original database and demonstrate that the apparent signal of increased risk is not predictive of clinically important differences. Should a differential signal of cardiac thromboembolic events persist, the sponsor was encouraged to consider proposing the use of lower doses of Uloric.

2. Due to the potential for drug-drug interactions when co-administered with other commonly used drug products for which xanthine oxidase plays a role in

metabolism, the sponsor was asked to perform drug-drug interaction studies with theophylline, azathioprine and mercaptopurine. It was noted, however, that should they choose to not perform these studies, co-administration of Uloric and these drugs would need to be contraindicated and risk minimization strategies might be needed to assure that concomitant use did not occur.

3. Due to the finding of hemorrhagic adverse events and elevated INRs in patients on Uloric and warfarin in the original database for the application, and questions concerning the reliability of the results of a pharmacokinetic study that specifically looked at warfarin interaction with Uloric, the sponsor was asked to further evaluate the potential for concomitant administration of warfarin and Uloric to result in hemorrhagic adverse events, and to further evaluate the potential for exposure to Uloric alone to result in these types of events.

4. Due to an absence of data to evaluate the induction potential of Uloric on human CYP P450 enzymes, the sponsor was asked to perform a study to provide this data either in vitro or in vivo.

5. Due to an inadequate methodology for the 80- and 120-mg strength tablets, the sponsor was asked to revise their dissolution testing and specific parameters were provided.

Finally, the letter requested that the sponsor provide data to demonstrate that Uloric impacts some other important outcome for gout patients, beyond the surrogate of uric acid levels. It noted, however, that "While this data would be helpful in making an assessment of risk-benefit considerations for approval, these data would be acceptable as a phase 4 commitment should the above deficiencies be adequately addressed prior to the availability of outcomes data."

A complete response to the approvable letter was received on February 17, 2006.

Lei Zhang, Ph.D., the pharmacokinetics and biopharmaceutics reviewer for this submission has determined that the sponsor has provided adequate responses to Items 2 through 5 to address those deficiencies. For Item 2, the sponsor has agreed to there being a contraindication in the package insert for co-administration of theophylline with Uloric. Additionally, they have committed to conducting a drug-drug interaction study as a post-marketing commitment to evaluate the concomitant administration of Uloric and theophylline. The protocol has already been submitted to the IND, and comments were sent to the sponsor on June 30, 2006. The sponsor also agreed to a contraindication for the concomitant use of azathioprine and mercatopurine with Uloric. They chose not to study these potential interactions due to the potential risk to subjects.

For Item 3, the sponsor provided additional information that allowed Dr. Zhang to conclude that, "...one cannot conclusively rule out an interaction based on this study [and]...A new warfarin interaction study with sufficient subjects to complete the trial is

needed for a conclusive determination." However, Dr. Zhang also notes, "With the current data, [redacted]

For Item 4, the sponsor has committed to conducting an in vitro human CYP induction study as a post-approval commitment.

For Item 5, the sponsor has accepted the Agency's recommendations for the final dissolution method and acceptance criteria for the 80- and 120-mg tablets.

In response to the clinical concerns noted in the approvable letter, the sponsor has provided a reanalysis of the safety data. This reanalysis was reviewed by Tatiana Oussova, M.D. and a secondary review was completed by Joel Schiffenbauer, M.D. The sponsor disagrees that there is a clinically relevant cardiovascular safety signal and has submitted an analysis based on readjudication of the original data (and including events that occurred after datalock for the original application) by an expert consultant, Dr. William White. Dr. White performed this readjudication of the possible cardiac thromboembolic adverse events blinded to treatment arm assignment. Dr. White reclassified some of the previously denoted cardiovascular events to non-cardiovascular categories and some of the APTC-classified events to non-APTC events and vice versa.

The review team consulted the Division of Cardio-Renal Products (DCRP) for an assessment of Dr. White's readjudicated cases. DCRP concluded that the sponsor's adjudication of the cases was not helpful due to a paucity of detail in the CRFs regarding the events and to an absence of appropriate criteria that would allow a fair and reasoned readjudication. As such, DCRP provided an adjudication of their own that was mostly based on the reporters' original diagnoses, and noted that all of the cases were serious, and all but one were cardiovascular adverse events. In addition, DCRP found that the sponsor had extended the APTC criteria into domains for which they had not been designed, making adjudication into an APTC or non-APTC category of little use.

Drs. Oussova and Schiffenbauer assessed the sponsor's reanalysis and the post-datalock adverse events and determined that, even in the most conservative of analyses, there remains an increased relative risk of cardiovascular thromboembolic adverse events in the Uloric-treated subjects compared to either the placebo- or allopurinol-treated subjects. Dr. Schiffenbauer notes that, "Just examining the 2 phase 3 controlled trial data, there is still a 3-4 fold excess of events…comparing febuxostat to allopurinol. Dr. Oussova has questioned the inclusion of "coronary revascularization" and "CHF" into a category of secondary APTC events in the sponsor's analysis, as they are common in the gout population and their addition into an analysis of cardiothrombolic events could dilute the results and obscure the possible risk of true thrombotic events. Dr. Oussova also found a number of instances in which the sponsor had inaccurately calculated the total number of events in a cardiovascular category.

The clinical team also reviewed the sponsor's response regarding the possibility of a drug-drug interaction between Uloric and warfarin. Dr. Schiffenbauer notes in his review:

> The clinical consequences of the use of warfarin in patients on febuxostat is difficult to interpret from the data presented. The initial NDA presented data on 2 patients who died with retroperitoneal hemorrhage. The first patient had a CT report that did not support a diagnosis of retroperitoneal hemorrhage, but did not rule out blood in the abdomen. The second patient likely did have a retroperitoneal hemorrhage but it is not clear if she was receiving febuxostat during her hospitalization.

Based on this information, and in agreement with Dr. Zhang, Dr. Schiffenbauer concluded that:

> ...the issue of the potential for febuxostat to interact with warfarin appears to hinge on the adequacy of the warfarin interaction study. If the study as was performed previously is considered to be acceptable, then the sponsor can be asked to follow up with collection of phase 4 data to further evaluate this issue...

The review team found that the sponsor's reanalysis of the remainder of the adverse events in the database did not shed any new light on the findings noted in the original application.

Discussion:

This complete response does not adequately address the cardiovascular safety concerns noted during the first review cycle for the application. While I think that some of Dr. Oussova's analyses may have overestimated the actual relative risk of cardiovascular thromboembolic events, I am convinced by the review team's assessment that a clear signal of risk remains, even in the most cautious analysis. Interpretation of the cardiovascular adverse events is difficult at best, as noted in my original memo. A paucity of detail and inadequate definitions for event categories hinders our ability to clearly delineate clinically relevant events. This is complicated by the relatively smaller number of exposures in the comparator groups due to uneven randomization in the controlled trials. Nevertheless, the apparent increase in cardiovascular thromboembolic adverse events in the Uloric-exposed subject population results in my continued concern that the risks associated with this product may outweigh the benefits. This is especially a concern for a product where the approval would be based on a surrogate (uric acid reduction), not on an outcome assessment. To approve a drug on such a surrogate when an unresolved signal of potential, serious adverse CV effects is outstanding does not appear warranted. The sponsor has not addressed our recommendation that they consider evaluating a lower dose of Uloric, which may not demonstrate the same high level of efficacy as the 80- and 120-mg strengths but which may result in a more acceptable safety profile.

The sponsor's complete response to the approvable letter also details a series of commitments to address the drug-drug interaction concerns raised by the review team that include contraindications in the package insert and post-marketing studies. These commitments will adequately address our concerns. However, in light of the fact that the clinical safety concerns have not been adequately addressed in their submission, the sponsor should begin the necessary drug-drug interaction studies as soon as possible.

The sponsor's commitment to use the Agency defined methodology and criteria for their dissolution testing is acceptable. A study to further assess clinical outcomes beyond the surrogate endpoint of reduced uric acid remains important to our understanding of the product's effectiveness.

Action:

Approvable

The sponsor needs to provide further data to clarify the cardiovascular risks of the proposed doses and/or provide data on the safety and efficacy of lower doses of febuxostat in order to assure us that a dose level(s) with favorable risk-benefit characteristics has been defined.

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II, CDER, FDA

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

/s/

Bob Rappaport
7/31/2006 08:38:03 PM
MEDICAL OFFICER

Robert Meyer
8/1/2006 08:49:06 AM
MEDICAL OFFICER
Agree with Dr. Rappaport's memo and this memo stands as the memorandum of record for this action cycle

CLINICAL REVIEW

Application Type	sNDA 21-856
Submission Number	033
Submission Code	Complete Response
Letter Date	02-17-2006
Stamp Date	02-21-2006
PDUFA Goal Date	08-21-2006
Reviewer Name	Tatiana Oussova, MD, MPH
Review Completion Date	July 17, 2006
Established Name	Febuxostat
(Proposed) Trade Name	Uloric
Therapeutic Class	Xanthine oxidase inhibitor
Applicant	Tap Pharmaceutical Product Inc.
Priority Designation	S
Formulation	Oral
Dosing Regimen	80 mg and 120 mg tablets once a day
Indication	Management of hyperuricemia in patients with gout
Intended Population	Adults

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends non-approvable action for febuxostat 80 mg and 120 mg tablets for the treatment of hyperuricemia in patients with gout based on an unfavorable risk/benefit profile. Initial review cycle raised concerns regarding the potential for febuxostat 80-mg and 120-mg doses to cause cardiovascular (CV)/thrombotic adverse events (AE) in excess of that seen with allopurinol or placebo. Reanalyses of existing data and additional analyses of new data did not eliminate safety concerns raised in initial review. Of further concern, the efficacy of febuxostat 80 mg and 120 mg was established based on a surrogate endpoint without sufficient evidence of clinical efficacy.

1.2 Recommendation on Postmarketing Actions

Not applicable since no approval is being recommended.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

There are no changes since original submission.

1.3.2 Efficacy

There are no new efficacy data provided with this submission.

1.3.3 Safety

With this resubmission the Sponsor addressed the issue raised during the initial review cycle regarding the potential for febuxostat to increase the risk of cardiovascular/thrombotic adverse events. Reanalyses of existing data included an adjudication of cardiovascular adverse events performed by a cardiologist Dr. White, in a blinded manner, and additional analyses of new data derived from ongoing long-term extension studies that factored differences in exposure between treatment groups into analysis.

It appears that there is a significant increase in risk of cardiovascular (CV) thromboembolic adverse events, including deaths, in a group of patients exposed to febuxostat compared to allopurinol or placebo groups. This increase in risk cannot be explained by differences in baseline characteristics such as baseline medical conditions or cardiovascular risk factors. This

increased risk persists after the differences in exposure between two treatment groups are incorporated into analysis. No dose-response effect was observed between febuxostat 80-mg and 120-mg doses.

The cut-off date for this resubmission was February 08, 2006. In this augmented database there were 10 deaths that occurred in febuxostat arm. Eight of those deaths were adjudicated by the Sponsor as cardio-vascular. There were two additional deaths since the cut-off date that were also adjudicated as cardiovascular. All 12 deaths occurred in febuxostat arm. There were no deaths in allopurinol arm.

Secondly, the rate of cardiovascular adverse events, both non-adjudicated and adjudicated, is consistently higher in febuxostat arm compared to allopurinol arm. This difference is noted in phase 3 studies and continues in long-term extension studies. The rate of CV adverse events in long-term extension studies appears lower in both arms compared to phase 3 studies, but this could be due to depletion of susceptible population. Also, the studies are still ongoing and final numbers are not available.

The Sponsor also addressed the issue of a possible risk of bleeding associated with concomitant use of febuxostat and anti-coagulant, warfarin in particular. The overall number of patients in the database is very small, and does not allow us to reach a definitive conclusion. It appears that the incidence of bleeding events increases slightly in all treatment groups when anti-coagulant is co-administered without evidence of a dose-response. Most of the bleeding events that occurred in all groups appear to be minor, such as nose bleeds or bruising. Two serious adverse bleeding events in patients taking concomitant anti-coagulant occurred in the febuxostat group. Two patients died from retroperitoneal hemorrhage while on concomitant febuxostat and warfarin. In addition one non-serious AE of rectal hemorrhage in a patient on concomitant febuxostat and warfarin/aspirin led to a study discontinuation. b(4)

The interaction between febuxostat and anti-coagulants cannot be excluded.

The analyses of augmented data on other serious adverse event, discontinuations due to adverse events, common adverse events, and adverse events associated with different systems did not produce new results.

1.3.4 Dosing Regimen and Administration

There are no changes to the dosing regimen or administration from original submission.

1.3.5 Drug-Drug Interactions

Please, see review by Dr. Lei Zhang

1.3.6 Special Populations

No new studies in special populations were performed.

2 INTRODUCTION AND BACKGROUND

The original NDA 21-856 was submitted to the FDA on December 14, 2004 for Uloric (febuxostat tablets) 80 and 120 mg that resulted in an approvable action. An approvable letter was sent to the Sponsor on 10-14-05.

The following items relevant to this safety review were listed in the FDA approvable letter under deficiencies:

1. Further evaluate the safety profile of Uloric, especially in regard to its potential to result in cardiovascular adverse events. Our review of the safety database submitted in your application raises concerns regarding the potential for Uloric to cause clinically significant cardiovascular/thrombotic adverse events in excess to that seen with allopurinol or placebo, even when exposure-over-time is factored into the analysis. This safety signal may be addressed by providing further comparative controlled clinical safety data or, possibly, through reanalyses of the current database (augmented by any recently completed or on-going studies) that demonstrate the apparent signal of increased risk is not predictive of clinically important differences. Should a differential signal of thromboembolic CV events remain upon the analysis of any new data and/or reanalyses of existing data, we would strongly encourage you to consider proposing the use of lower doses of Uloric, rather than those proposed.

2. 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.

An additional meeting between the Agency and the Sponsor was held on 12-05-2005 to clarify deficiencies identified in the approvable letter. On February 22, 2006 The Sponsor responded to the approvable letter with a complete response to all deficiencies identified by the FDA.

As a part of the complete response that addresses the issue of cardiovascular safety, the Sponsor submitted the reanalyses of existing data augmented by new data from two ongoing long-term

extension studies TMX-01-005 and CO2-021 with a cutoff date of 8 February, 2006. Reanalyses of the updated database were performed with an emphasis on cardiovascular adverse events.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

See original reviews.

See review by Dr. Lei Zhang.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

The most important concern raised in the approvable letter was related to an increased risk of cardiovascular (CV) adverse events (AE) in febuxostat-exposed patient population. To address the Agency's concern, the Sponsor evaluated the safety data to determine the incidence of CV adverse events as defined by Antiplatelet Trialists' Collaboration (APTC). APTC events were further classified into primary that included cardio-vascular death, non- fatal myocardial infarction (MI) and non-fatal stroke, and secondary that included angina, coronary revascularization, transient ischemic attack (TIA), venous or arterial vascular thrombotic events, and congestive heart failure. All CV serious adverse events in the database were adjudicated by Dr. William White in a blinded fashion. Per the FDA request, the analysis of adjudicated and non-adjudicated APTC events was done separately for phase 3 studies, long-term studies, and combined phase 3 studies and long-term studies.

Since exposure to febuxostat and allopurinol in the controlled portions of the phase 3 studies was comparable, no adjustment for the difference in exposure was necessary. In long-term open-label studies, exposure to febuxostat is significantly greater than to allopurinol, therefore the exposure was factored into analyses that included the extension period.

Since the drug is not being marketed, there are no post-marketing data to review.

Of note, this review is based on the Sponsor's provided adjudication of CV adverse events. This reviewer believes that the Sponsor –provided adjudication of adverse events is not the most conservative assessment for the following reasons:

- It was done post hoc. Since it was done post-hoc, no attempts to collect incomplete data could be made making the adjudication of a number of adverse events difficult.
- It was done by a single Sponsor-hired cardiologist versus a group of independent adjudicators.

According to the Sponsor's adjudication of CV adverse events, 25 investigator-reported CV events were re-classified into non-CV event group. A number of CV events were re-classified from non-APTC into APTC and vice versa. This reviewer consulted with Cardio-Renal Division on events that were re-classified from APTC to non-APTC (5 events) and from non-APTC to APTC (6 events). The Cardio-Renal Division recommendation is to utilize investigator-reported

diagnoses when there is not enough information to adjudicate a reported diagnosis. This consult is included in the **Appendix 2.**

5 CLINICAL PHARMACOLOGY

See original review

No new data are submitted

6 INTEGRATED REVIEW OF EFFICACY

See original review

No new efficacy data are submitted

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

7.1.1.1 All-cause Mortality

Eight deaths (all in febuxostat arm) were previously reported in the original ISS or 4-Month Safety Update with the cutoff date of October 29, 2004. Four patients died during the Phase 3 randomized controlled studies and four patients died in the long-term extension studies. This submission has updated information with the cutoff date of February 08, 2006 and includes four additional deaths in the febuxostat arm from long-term extension study C02-021.

Below are the narratives of four patients that died since the original NDA review.

One death was attributed to metastatic colon cancer (subject 4343), three deaths were attributed to myocardial infarction (Subjects 4050, 4959 and 4136, all febuxostat 80 mg).

Subject 4959
Age: 73
Race: Caucasian
Gender: Male

Significant Medical History: Congestive heart failure, ischemic heart disease, coronary heart disease, 2 myocardial infarctions, biventricular pacemaker with OCD device insertion
Social History: Former smoker, family history of coronary artery disease
Concomitant Medications at the time of the event: Amiodaron, paracetamol, furosemide, potassium replacement, carvedilol, spironolactone, warfarin, eplerenone.
Study Drug History:
C02-009 Dosing: Febuxostat 120 mg QD
C02-021 Dosing: Day 1-64: febuxostat 80 mg QD/prophylaxis Day 65-312: febuxostat 80 mg QD
On Day 366 (53 days after the last dose of study drug) the subject was hospitalized with end-stage congestive heart failure (MedDRA Term: Cardiac failure congestive) which was fatal. Approximately 9 days prior to admission for this event, the subject was hospitalized for a non-ST segment elevation myocardial infarction. Approximately 3 days after discharge, the subject was re-admitted for abdominal pain, diarrhea, congestive heart failure, a BUN of 55 mg/dL, creatinine of 2.8 mg/dL, potassium of 5.6 mmol/L, AST 106 U/L, bilirubin 1.6 mg/dL and BNP of 2780. Urinary output was low despite treatment with iv fluids and furosemide. Three days after hospitalization, the subject experienced a worsening of his CHF with low systolic blood pressure of around 80-90 mmHg and hypoxia. He was transferred to an ICU where he was treated with dobutamine, dopamine and levophed. The subject's hypotension continued to worsen and he developed shock liver type transaminases with an ALT of 1821 U/L and an AST of 2783 U/L. The subject was subsequently intubated. The subject's family decided to continue supportive care but to avoid heroic measures. The subject's condition continued to decline and he expired on day 369. The death certificate listed the cause of death as cardiac pulmonary arrest, end stage congestive heart failure and respiratory failure (MedDRA Terms: Cardiac failure congestive, Cardio-respiratory arrest, respiratory failure).
Prior to these events, the subject experienced serious adverse events of pneumonia (MedDRA Term: Pneumonia) and worsening CHF (MedDRA Term: Cardiac failure congestive) on Day 13, and serious adverse events of exacerbation of CHF (MedDRA Term: Cardiac failure congestive-condition aggravated) and 3-vessel coronary artery disease (MedDRA Term: Coronary artery disease) on Day 256.

Subject 4343
Age: 59
Race: African-American
Gender: Male
Significant Medical History: Prostate cancer, recurrent umbilical hernia.
Social History: Unremarkable.
Concomitant Medications at the time of the event: Digoxin, quinapril, aspirin, meclozine.
Study Drug History:
C02-009 Dosing: Febuxostat 80 mg QD
C02-021 Dosing: Day 1-58: febuxostat 80 mg QD/prophylaxis Day 59-408: febuxostat 80 mg QD
On study day 409, the subject was diagnosed with colon cancer with liver metastasis (MedDRA Term: Colon cancer metastatic). One month prior to this, the subject complained about

abdominal pain. Laboratory results showed increased liver transaminases and a CT scan showed widespread hepatic metastatic disease with a finding in the cecum suspicious of a primary tumor. Biopsies performed during a colonoscopy revealed a moderate to poorly differentiated adenocarcinoma in the proximal ascending colon. The study drug was discontinued and 2 weeks later the subject underwent partial colectomy. The initial postoperative course was unremarkable but later the subject developed hyperbiliribinemia (bilirubin of 8.3 mg/dL) and a stent was placed. Subsequently, the subject developed profound rigor and chills and a blood culture revealed Gram-negative bacteremia. The subject was started with antibiotics. The subject subsequently died on day 454. No death certificate was available, but the investigator felt the cause of death to be related to complications of metastatic colon cancer.

Subject 4050 (Study C02-021) was a 72-year-old male with a medical history of hypertension, cardiac arrhythmia, and hypercholesterolemia. A few days prior to his death, the subject was seen by the investigator and complained about a "heavy feeling" in his arms. While cardiac enzymes were negative at that time, the ECG showed signs of ischemia. The subject died in his sleep at home on Day 803. The death certificate indicated probable myocardial infarction as the cause of death.

Subject 4136 (Study C02-021) was an 85-year old male with a history of coronary artery disease, hypertension, atrial fibrillation, and status post pacemaker insertion. On Day 788, the subject died at his home. The death certificate indicated acute myocardial infarction as the cause of death.

Two additional deaths were reported by the Sponsor in patients who did not take any study drug and therefore were not included in the tables:

1. One subject (Screening number 836902) died of a myocardial infarction during the screening/washout period of Study TMX-00-004 prior to randomization.

2. In a small magnetic resonance imaging (MRI) validation study in subjects with palpable gouty tophus/tophi (TMX-01-013) in which no study drug was administered, 1 subject (Subject 310) died from possible arrhythmia during the study.

Another patient (K007-22) died in the Japan development program due to ruptured aneurysm. The patient was randomized to Febuxostat 10 mg QD however it is unclear whether or not this patient took any dose of medication. The death occurred on the date the drug was scheduled to start. This death was never reported to regulatory authorities by the Sponsor.

The updated results are summarized in **Table 1**.

Table 1 (Sponsor's Table 2.0.a) Updated All-Cause Mortality in Febuxostat Clinical Program by Patient-Years of Exposure with Data as of 08 February 2006

Treatment	Patient-Years of Exposure	Number of Deaths	Rate Per 100 Patient-Years	95% Confidence Interval
Phase 3 Randomized Controlled Studies				
Febuxostat Total	671	4	0.60	0.162-1.526
Allopurinol 300/100 mg QD	334	0	0.0	0.000-1.105
Long-Term Extension Studies				
Febuxostat Total	2121	8	0.38	0.163-0.743
Allopurinol 300/100 mg QD	145	0	0.0	0.000-2.538
Phase 3 Randomized Controlled and Long-Term Extension Studies				
Febuxostat Total	2792	12	0.43	0.222-0.751
Allopurinol 300/100 mg QD	479	0	0.0	0.000-0.770

Note: No subjects died in the Phase 1 studies or during treatment in the Phase 2 controlled clinical trial (TMX-00-004).
The confidence intervals are calculated based on Poisson distribution.

Overall, in the Phase 3 randomized controlled studies and long-term extension studies, 12 subjects died; all subjects who died were randomized to 1 of the febuxostat treatment groups. The **death rate per 100 PY was 0.60 in the febuxostat groups and 0 in allopurinol group in phase 3 controlled studies; 0.38 for febuxostat versus 0 for allopurinol in long-term extension studies and 0.43 in the febuxostat group versus 0 in the allopurinol group in all studies combined.** Of note, exposure to febuxostat (**2792 patient-years**) was greater than exposure to allopurinol (**479 patient-years).**

Reviewer's comments:

- *Review of all-cause mortality revealed an inappropriately high number of deaths among patients exposed to febuxostat. The death rate in febuxostat group was highest in Phase 3 controlled studies (0.60) and somewhat less in long-term studies (0.43). One plausible explanation for this is that a subgroup of the most vulnerable patients dropped out of the study during the blinded phase due to either death or adverse event.*

7.1.1.2 Cardiovascular Mortality

The Sponsor provided an adjudication and assessment of cardiovascular adverse events performed by cardiologist, Dr. William White. The following patients ID's were adjudicated as cardio-vascular: K007-22, 2091, 2403, 2487, 2695, 4186, 4479, 4959, and two additional deaths reported by the investigator as due to myocardial infarction were adjudicated by the reviewer as cardio-vascular as well (4050, 4136).

Table 2 below lists all deaths in febuxostat clinical program as of 08 February, 2006 as adjudicated by the Sponsor.

Table 2.

Study No. /Phase	Subject/Age/Gender	Adverse Event	APTC/non-APTC
Febuxostat 80 mg QD			
C02-010/3	2019/77/Male	Retroperitoneal Hemorrhage	APTC
C02-010/3	2487/65/Male	Heart, Renal, Respiratory Failure	APTC
C02-021/3	4087/84/Male	Sepsis	Non-APTC
C02-021/3	4050/72/Male	Myocardial Infarction	ATPC
C02-021/3	4136/85/Male	Acute Myocardial Infarction	APTC
C02-021/3	4959/73/Male	Myocardial Infarction	APTC
C02-021/3	4343/59/Male	Metastatic Colon Cancer	Non-APTC
Febuxostat 120 mg QD			
C02-010/3	2403/68/Male	Respiratory /Cardiac Arrest post-op	APTC
C02-010/3	2461/74/Male	Metastatic Colon Cancer	Non-APTC
C02-021/3	4479/75/Male	Acute Myocardial Infarction	APTC
C02-021/3	2695/60/Male	Myocardial Infarction	APTC
C02-021/3	4186/84/Female	Retroperitoneal Hemorrhage	APTC

The updated results for cardiovascular mortality adjusted for exposure are summarized in **Table 3** below.

Table 3 (Sponsor's Table 4.0.a). Updated Treatment-Emergent Cardiovascular Deaths in Combined Phase 3 Randomized Controlled and Long-Term Extension Studies with Data as of 08 February 2006

	Treatment						
	Placebo	Febuxostat					Allopurinol
Number of CV Deaths	(N=134) (PY=59.9)	Total (N=1692) (PY=2791.8)	40 mg (N=12) (PY=34.6)	80 mg (N=1221) (PY=1697.1)	120 mg (N=909) (PY=1006.1)	240 mg (N=134) (PY=54.0)	300/100 (N=642) (PY=479.1)
	0	9	0	5	4	0	0
Per 100 PY	0	0.32	0	0.29	0.40	0	0
95%CI[a]	(0–6.16)	(0.147-0.612)	(0–10.67)	(0.096-0.688)	(0.108-1.02)	(0–6.83)	(0-0.77)

Studies included: TMX-01-005, C02-009, C02-010, and C02-021.

a 95% CI were calculated based on Poisson distribution.

Reviewer's comments:

- *The Sponsor miscalculated the total number of APTC deaths in febuxostat arm. Three APTC deaths occurred during phase 3 controlled studies (at a **rate of 0.45 per 100 PY**) and 7 additional APTC deaths occurred in long-term extension studies with the **overall rate of 0.36 per 100 PY**. The incidence of deaths in the allopurinol group is 0.*

- *The CV mortality rate is only slightly lower in long-term extension studies compared to the controlled portions of the phase 3 studies*

- *Even though cardio-vascular fatal events are expected in the general population, and more so in a population of patients with gout due to multiple CV risk factors, one cannot assume those events are due to underlying disease or intercurrent illness, and not the drug. Thus, a comparison with a control group is very important. In this case, the comparator drug is allopurinol with the mechanism of action similar to that of febuxostat. There were no differences in background characteristics between the two groups. Therefore, any difference in efficacy results or safety profile that is seen between the two drugs can be attributed to the drug itself. Comparison between febuxostat and allopurinol suggests that there is an excess risk of*

all-cause mortality and cardiovascular mortality among patients who took febuxostat. This difference in risk persists after differences in exposure are taken into account. No dose-related increases in cardio-vascular events were observed on febuxostat. These results are consistent with the original NDA analysis.

7.1.2 Other Serious Adverse Events

The safety database was updated to present additional data from the febuxostat ongoing long-term extension studies. The 4-Month Safety Update, which was submitted on 14 April 2005, included safety data collected through 29 October 2004 and serious adverse event (SAE) data collected through 31 December 2004. This updated database includes safety data and SAEs collected through 16 November 2005. It contains additional data from the 2 long-term, open-label extension studies (TMX-01-005 and C02-021) compared to the previous submission.

In the long-term extension studies, the allopurinol 300/100-mg once daily (QD) treatment group has a smaller number of subjects and shorter treatment duration than those in the febuxostat 80-mg QD and febuxostat 120-mg QD treatment groups due to the study design, which included an imbalanced randomization with more patients in febuxostat treatment group. In order to adjust for the differences in duration of exposure among treatment groups, the Sponsor summarized adverse events in the long-term extension studies by patient-years of exposure (PY) as agreed to with the FDA on 5 December 2005.

There were 4 treatment groups in the long-term extension studies: febuxostat 40 mg QD, febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD. However, there were only 12 subjects in the febuxostat 40 mg QD treatment group. Thus, the primary focus of the discussion in this safety update includes the febuxostat 80-mg QD, febuxostat 120-mg QD (which are also the doses for which th4e Sponsor seeks approval) and allopurinol 300/100-mg QD treatment groups.

The Phase 3 randomized controlled studies (C02-009 and C02-010) were presented in the original ISS and no new data are available. All new analyses that were performed for the Phase 3 randomized controlled studies for cardiovascular events and bleeding events will be discussed under CV events section.

Due to specifics of the study design subjects starting on a given treatment in the long-term extension studies could be switched to another treatment, and thus a subject might have received more than 1 treatment regimen during the study. Handling of treatment switches in the analyses of the long-term extension studies is described as the following:

- Study drug exposure for each treatment group is based on the actual treatment that subjects received during the study for the time period or duration presented. The study

drug exposure summarized under the Febuxostat Total column is cumulative for febuxostat exposure, regardless of the specific dose. For example, consider a subject who initially receives 6 months of febuxostat 120 mg and then receives 9 months of febuxostat 80 mg. This subject has received febuxostat (at some dose) for a total of 15 months. This subject is included in the Febuxostat Total column as receiving 15 to 18 months of exposure; however, in each of the febuxostat 80 mg and 120 mg columns the subject would only be included as receiving 6 to 9 months of exposure.

- In all summary tables presented, the total number of subjects presented for each treatment group (N) represents the total number of subjects receiving that treatment regimen during the study. Since a subject might have received more than 1 treatment regimen because of treatment switches, the total number of subjects presented for the Febuxostat Total column is the total number of unique subjects receiving febuxostat and is lower than the total number of subjects for each of the treatment groups combined.
  Similar to the total number of subjects (N) presented for each treatment group in all summary tables, the total patient-years of exposure for each treatment group represents the total exposure for all subjects receiving that treatment regimen during the study. However, the total patient-years of exposure presented for the Febuxostat Total column is the sum of patient-years of exposure for all febuxostat treatment groups.

- In all analyses, events and evaluations are assigned to the treatment the subject was receiving at the time of events/evaluations occurrence. These include adverse events, premature discontinuations, mortality, vital signs, laboratory evaluations, and ECGs.

Table 4 (Sponsor's Table 3.4.a). Incidence of Serious Adverse Events per 100 Patient-Years of Exposure in Long-Term Extension Studies and Phase 3 Randomized Controlled Studies

Long-Term Extension Studies	–	Febuxostat					Allopurinol 300/100 mg QD (N=178) (PY=133.3)
		Total (N=1143) (PY=1933.7)	40 mg QD (N=12) (PY=33.0)	80 mg QD (N=910) (PY=1265.4)	120 mg QD (N=522) (PY=635.3)	–	
Phase 3 Randomized Controlled Studies	Placebo (N=134) (PY=59.9)	Total (N=1177) (PY=671.1)	–	80 mg QD (N=523) (PY=312.6)	120 mg QD (N=520) (PY=304.5)	240 mg QD (N=134) (PY=54.0)	Allopurinol 300/100 mg QD (N=521) (PY=333.7)
Treatment-Emergent SAEs per 100 PY							
Long-Term	--	9.5	21.2	9.9	8.0	–	11.3
Phase 3	5.0	11.6	--	11.8	11.5	11.1	8.1
Treatment-Related SAEs per 100 PY							
Long-Term	--	0.3	0	0.3	0.2	–	0
Phase 3	0	0.1	--	0	0	1.9	0

SAE = serious adverse event; PY = patient-years of exposure
Long-term extension studies included: TMX-01-005 and C02-021
Phase 3 randomized controlled studies included: C02-009 and C02-010
Cross-reference: Statistical Tables 3.1.10, 3.1.11, 3.2.10, and 3.2.11