

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Arthritis Advisory Committee

November 24, 2008

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Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Rheumatology Products

MEMORANDUM

DATE: October 22, 2008

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

TO: Chair, Members, and Invited Guests
Arthritis Advisory Committee (AAC)

RE: Overview of the November 24, 2008 AAC Meeting to Discuss
NDA 21-856 for febuxostat (Uloric) for the treatment of
hyperuricemia in patients with gout

Febuxostat is a xanthine oxidase inhibitor developed to lower serum uric levels in patients with gout. Patients with gout who have recurrent episodes of gouty arthritis or who develop tophi (deposits of uric acid in tissues) are treated with drugs to reduce uric acid levels. The clinical development program for febuxostat included studies of 40 mg, 80 mg and 120 mg doses. If approved, febuxostat would be the second xanthine oxidase inhibitor marketed in the United States. Febuxostat is proposed for use at a dose of 40 mg or 80 mg orally daily.

The Applicant, Takeda, Inc., has submitted data for efficacy of both the 40 and 80 mg doses. The Agency does not dispute efficacy of febuxostat at these doses. Rather, the Agency presentation will focus on safety issues identified during review of the application. During review of the initial two Phase 3 studies the Agency determined that there was a higher rate of several serious adverse events in patients receiving febuxostat. Patients receiving febuxostat had a higher rate of overall mortality, mortality from cardiovascular causes, and a higher rate of cardiovascular thromboembolic adverse events. Because of the small numbers of events in each study arm there was uncertainty concerning whether the adverse events represented a genuine safety signal or whether they may have occurred by chance. Due to the concern about a possible cardiovascular

safety signal the Agency informed the Applicant that febuxostat could not be approved without additional information on the cardiovascular safety of febuxostat.

The Applicant subsequently conducted an additional Phase 3 trial that assessed safety and efficacy of the 40 and 80 mg doses and those results will be presented at the advisory committee meeting. Briefly, this new study did not show a cardiovascular safety signal.

During this meeting, you will initially hear two presentations: one on gout and cardiovascular risks in patients with gout; the second on interpreting potential safety signals with small numbers of events. Then representatives from the Agency and the applicant, Takeda, Inc., will present:

- the clinical development program for febuxostat; and
- data from the clinical trials performed to assess the safety and efficacy of febuxostat.

Following these presentations, you will be asked to assess these findings and to discuss the apparent risks and benefits of febuxostat. We will ask the committee to address whether the evidence indicates that there is a cardiovascular safety signal for the 40 mg and for the 80 mg dose. We will ask the committee to discuss the efficacy and clinical utility of each proposed dose. We will ask the committee to consider the patient population with renal impairment and discuss whether this population represents an unmet medical need population for uric acid lowering therapies and to discuss the safety, efficacy and clinical utility of febuxostat in this patient population. We will ask the committee whether the Applicant has presented adequate data to determine whether the potential benefits of febuxostat outweigh the potential risks. Finally, we will ask the committee what postmarketing studies would be appropriate if febuxostat is approved.

The Division and the Agency are grateful to the members of the committee and our invited guests for taking time from your busy schedules to participate in this important meeting. Thank you in advance for your advice, which will aid us in making the most informed and appropriate decision possible.



**Briefing Document for the
Arthritis Advisory Committee Meeting**

November 24, 2008

**Uloric®/febuxostat
NDA 21-856**

Department of Health & Human Services

**Food & Drug Administration
Center for Drug Evaluation & Research
Division of Anesthesia, Analgesia and Rheumatology Products
Silver Spring, MD 20993**

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I. Background

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.

In the United States, there is a self-reported prevalence of 1.4% in men and 0.6% in women, as of 1986. 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. The overall prevalence has been increasing over time.

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”¹ 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 results in 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.

Treatment and prevention of gout has traditionally involved anti-inflammatory medication for acute attacks (e.g., colchicine, corticosteroids or nonsteroidal anti-inflammatories), 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

¹ Harrison's Principles of Internal Medicine. Thirteenth Edition. p. 2079.

urate level. Prolonged treatment is believed to reduce gouty flares and to lead to the resolution of large tophi. However, 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%. Since patients with renal impairment may develop toxicities on normal doses, it is usually recommended that the dose of allopurinol be reduced for patients with a decreased creatinine clearance; this further reduces the efficacy in this population.

Febuxostat is a non-purine selective XO inhibitor which according to the Applicant inhibits both oxidized and reduced forms of XO. Accordingly, the Applicant contends that febuxostat is at least as potent as allopurinol in general and more efficacious in patients with renal impairment. The proposed label states that “no dose adjustment is necessary when administering ULORIC to patients with mild to moderate renal or hepatic impairment.” Febuxostat is to be used for the treatment of chronic gout. Two doses of febuxostat 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.”

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.² 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 death; relative risk, 3.12 (95% confidence interval 0.92-10.6); . . .). Likewise men

² Abbott, Robert et. al. “Gout and Coronary Heart Disease: The Framingham Study.” J Clin Epidemiol. Vol 41, No. 3, pp. 237-242, 1988

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).....³

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 arms than in the control arms. Consequently, an Approvable letter was issued 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.”

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 C01-010, 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) criteria in conjunction with consultation by a cardiologist Dr. William White. The APTC criteria were utilized to provide a consistent approach to identifying cardiovascular events. APTC criteria were applied first to *investigator-reported* events and, second, to events that were *adjudicated* by Dr. White.

To identify investigator-reported events that correspond to APTC criteria, 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

³ 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.

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 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, and (4) application of APTC criteria and adjudication was introduced in a post hoc fashion. Thus there was uncertainty about whether the findings definitely represented an 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 committee (the Cardiovascular Endpoints Committee) was formed to perform adjudication of potential cardiovascular events. The committee 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, randomized, 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 80 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 the febuxostat arms as compared to the control arms. Therefore, the agency issued an Approvable letter requesting additional data or a reanalysis of the available data to address whether there is an increased risk of cardiovascular thromboembolic events with febuxostat. 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.

The Applicant reassessed the safety data and determined the incidence of cardiovascular adverse events as defined by APTC criteria. 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 cardiovascular safety signal with febuxostat. The areas of concern as described in that review are outlined below.

1. All cause mortality

Review of the deaths occurring in the febuxostat clinical development program revealed that all the deaths were seen in febuxostat-treated patients. As shown in Table 2, there were 4 deaths in RCTs: all were in febuxostat treated patients and none were in the active-control allopurinol arm. The mortality rate, in RCTs, was 0.60/ 100 patient years among febuxostat treated patients. In the long-term extension studies (LTES) the mortality rate was 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 the mortality rate in the febuxostat group is numerically higher compared to the allopurinol group, it is not possible to reach definitive conclusions about the risk of all-cause mortality between the two treatment arms because of the small number of events.

2. Cardiovascular Mortality.

Table 3 presents the results from the analysis of RCTs and the LTES. Compared with allopurinol, there were more cardiovascular deaths in the febuxostat arm. Of the 9 deaths in the febuxostat arm, 3 were from the RCTs and 6 were from the LTES. It should be noted, however, that exposure to febuxostat was considerably greater than exposure to allopurinol (2791.8 vs. 479.1 patient years) because most of the 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

Number of CV Deaths	Treatment						
	Placebo (N=134) (PY=59.9)	Febuxostat					Allopurinol 300/100 (N=642) (PY=479.1)
		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)	
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 those 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					Allopurinol 300/100 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 =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: the Antiplatelet Trialists Collaboration (APTC) criteria. Two types of analyses were undertaken. The first analysis explored all investigator-reported events that met APTC criteria (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 met APTC criteria.

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: Incidence Rates and Confidence Intervals for Subjects with Investigator-Reported Treatment-Emergent Primary APTC Events in the Phase 3 Randomized Controlled Studies

Primary APTC Events	Treatment Group, n (%)					
	Placebo (N=134)	Febuxostat				Allopurinol (N=521)
		Total (N=1177)	80 mg QD (N=523)	120 mg QD (N=520)	240 mg QD (N=134)	
Overall 95% CI ^a	0 (0.00-2.71)	9 (0.8) (0.35-1.45)	4 (0.8) (0.21-1.95)	5 (1.0) (0.31-2.23)	0 (0.00-2.71)	1 (0.2) (0.005-1.07)
CV death 95% CI ^a	0 (0.00-2.71)	3 (0.3) (0.053-0.74)	2 (0.4) (0.046-1.37)	1 (0.2) (0.005-1.07)	0 (0.00-2.71)	0 (0.00-0.706)
Non-fatal myocardial infarction 95% CI ^a	0 (0.00-2.71)	5 (0.4) (0.14-0.99)	2 (0.4) (0.046-1.37)	3 (0.6) (0.119-1.68)	0 (0.00-2.71)	1 (0.2) (0.005-1.065)
Non-fatal stroke 95% CI ^a	0 (0.00-2.71)	1 (0.08) (0.002-0.47)	0 (0.00-0.70)	1 (0.2) (0.005-1.07)	0 (0.00-2.71)	0 (0.00-0.706)
Non-fatal cardiac arrest 95% CI ^a	0 (0.00-2.71)	1 (0.08) (0.002-0.47)	0 (0.00-0.70)	1 (0.2) (0.005-1.07)	0 (0.00-2.71)	0 (0.00-0.706)

Studies included: C02-009 and C02-010

Adverse events summarized were reported after the first dose of study drug and within 30 days of the last dose of study drug.

^a CI calculated based on binomial distribution

Source: Complete Response to October 14, 2005 Approvable Letter, p. 25.

The overall rate of investigator-reported APTC events is higher in the febuxostat group compared with the allopurinol group; among all 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 (95% CI of 0.5, 32). The confidence interval includes the null value and values that correspond to a more favorable outcome with febuxostat than with allopurinol, so that 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.⁴ 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).

⁴ 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 rate of cardiovascular thromboembolic events using the more inclusive criteria of investigator-reported primary and secondary APTC events. Events were observed more frequently in the febuxostat group than with allopurinol. The most common events in the febuxostat group were angina, revascularization and non-fatal MI. Except for revascularization, all events were seen at a higher rate with febuxostat compared with allopurinol and placebo.

Table 7: Incidence Rates and Confidence Intervals for Subjects with Treatment-Emergent Primary and Secondary Investigator-Reported APTC Events in the Phase 3 Randomized Controlled Studies

Primary and Secondary APTC Events	Treatment Group, n (%)					
	Placebo (N=134)	Febuxostat				Allopurinol 300/100 mg QD (N=521)
		Total (N=1177)	80 mg QD (N=523)	120 mg QD (N=520)	240 mg QD (N=134)	
Overall	1 (0.7)	25 (2.1)	13 (2.5)	11 (2.1)	1 (0.7)	7 (1.3)
95% CI ^a	(0.019-4.09)	(1.38-3.12)	(1.33-4.21)	(1.06-3.75)	(0.019-4.09)	(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 the APTC criteria. The results of this reanalysis constitute the 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

	Placebo (N=134)	Treatment Group Febuxostat			Allopurinol 300/100 mg QI (N=521)	
		Total (N=1177)	80 mg QD (N=523)	120 mg QD (N=520)		240 mg QD (N=134)
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)	(0.005-1.07)
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 rate of events in the febuxostat 80 mg group remains approximately four times that of allopurinol (95% CI 0.4, 36); the rate 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 favorable outcome with febuxostat than with allopurinol, so that the direction of the difference in risk if any is 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 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)	
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 investigator-reported APTC events or by post-hoc adjudication by a cardiologist.

Although a concern was raised about cardiovascular safety, there are limitations in the data that raise uncertainty about the conclusions. First, many of the comparisons involve small numbers of events. Second, exposure to allopurinol in the LTES was limited since most patients in the LTES received open-label febuxostat. The long-term extension studies contained 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 higher rate of death and cardiovascular thromboembolic events in the febuxostat group suggests that febuxostat may be associated with an increased cardiovascular risk, the limitations described above make 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 and conduct:

The principal 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 and 80 mg, in comparison with allopurinol 300 mg or 200 mg in subjects with gout and hyperuricemia. A total of 2269 subjects were enrolled and randomized 1:1:1 to each arm. Whether they received 300 mg or 200 mg of allopurinol was determined by baseline renal function. At least 65% of the subjects in this study had mild-to-moderate renal impairment (with creatinine clearance of 30-89 mL/min).

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

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 study visit four days before start of the study. The demographic data as well as medical history is given in Table 10. No significant imbalances between study arms were noted.

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.

B. Efficacy

Table 12 summarizes efficacy results for all four RCTs: the three previously reported and reviewed by FDA during the second cycle and the most recent one, study F-153. 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 trials where there was an allopurinol arm for comparison, this comparison achieved statistical significance.

Table 12: Proportion of Subjects with sUA Levels < 6.0 mg/dL at the Final visit

Study Number	Febuxostat 40 mg QD	Febuxostat 80 mg QD	Allopurinol 300 mg QD ^a	Placebo
F-GT06-153	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-00-004	56% [#] (19/34)	76% [#] (28/37)	N/A	0% (0/35)

N/A = not applicable (dose/treatment was not evaluated).

^a In Study F-GT06-153, 145 allopurinol subjects were dosed at 200 mg QD. In Study C02-009, 10 allopurinol subjects were dosed at 100 mg QD.

* Indicates statistical significance versus allopurinol at p<0.001.

† Indicates statistical significance versus febuxostat 40 mg QD at p<0.001

‡ Noninferior to allopurinol using the lower bound of the 95% confidence interval of the difference (-1.9%) being greater than the critical value of -10%.

Indicates statistical significance versus placebo at p<0.001.

Source: Complete Response to 02 August 2006 Approvable Letter, p. 22.

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. As shown in Table 12, 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. The Applicant's analyses demonstrated non-inferiority of febuxostat 40 mg to allopurinol.

A secondary endpoint of Study F-153 was to assess 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 \geq 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. The table below 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 13: Proportion of Moderate/Mild Renally Impaired Subjects Whose Final Visit Serum Urate Level was < 6.0 mg/dL (ITT subjects)†. Study F-GT06-153

Final Visit Serum Urate Level <6.0 mg/dL	Febuxostat 40 mg QD (N=479)	Febuxostat 80 mg QD (N=503)	Allopurinol 300/200 mg QD (N=501)
	n (%)	N (%)	N (%)
	238 (49.7)	360 (71.6)	212 (42.3)
	Difference in Proportions	95% CI ^a	p-value ^b
Febuxostat 40 mg vs Allopurinol	7.4%	(1.1%, 13.6%)	0.021*
Febuxostat 80 mg vs Allopurinol	29.3%	(23.4%, 35.1%)	<0.001***
Febuxostat 40 mg vs Febuxostat 80 mg	21.9%	(15.9%, 27.8%)	<0.001***

CI=confidence interval.

a 95% CI = 95% confidence interval for the difference in proportions based on the normal approximation for the binomial distribution.

b p-value from a Fisher's exact test.

*, *** Statistically significant difference at the 0.05 and 0.001 level, respectively.

Source: Complete Response to 02 August 2006 Approvable Letter, p. 23.

† 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 statistically non-inferior to allopurinol. Moreover, 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.

C. 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 C0-009 and C0-010 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 of cardiovascular disease: approximately 1300 subjects enrolled with a prior cardiac history disease. 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 (Table 14) 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 favorable outcome with febuxostat than with allopurinol, so that 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.

Table 14: 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 15 presents data on mortality rates in Study F-153 and aggregate data from all randomized and long-term extension studies. 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%). The rate of mortality with febuxostat (0.38/100 pt-yrs) in the long-term extension studies updated with an additional 500 patient-years of exposure is similar to the rate reported in the second cycle submission (see Table 2).

Table 15: All-Cause Mortality in Febuxostat Clinical Program by Patient Years of Exposure

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.

In the previous 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 671 years of patient years of exposure) in the febuxostat arm (rate of 0.6% compared with 0 deaths (in 334 years of patient exposure) in the allopurinol arm (Table 2). In the long-term extension studies there had been 8 deaths in the febuxostat arm (2121 patient years of exposure) compared with 0 in the allopurinol arm, as of the 2006 submission. Since that time there have been two additional deaths in the ongoing LTES.

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 16 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 16: 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/ .25%	0
F-GT06-153		
N	1513	755
Number/% with CV Mortality by MedDRA preferred term	0	2/ .26%
*Cross reference: Tables 8 and 17		
**C0-009 and C0-010		

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 stated previously, investigator-reported events were identified by mapping MedDRA Preferred Terms into 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 17 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 an event rate of 0, 0.1 and 0.4%. For the combined febuxostat arms the event rate was 0.06%. Regarding secondary investigator-reported APTC events, the event rates were similar in the three study arms. In summary, the rates of primary and secondary APTC events were not increased in the febuxostat arms compared to allopurinol.

Table 17: 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 18 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 event rates are somewhat lower with the 2008

data compared to the 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.

Table 18: Investigator-Reported APTC Events in Long Term Studies

Investigator-Reported Primary and Secondary APTC events in Long Term Extension Studies *						
	Primary APTC Events					
	<i>Febuxostat 80 mg</i>		<i>Febuxostat - total</i>		<i>Allopurinol 300/100</i>	
	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: data are 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 meeting APTC criteria. A committee of 3 individuals adjudicated, in a blinded fashion, 319 events. As seen in Table 19, 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 19: 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.

In the division's review of the cardiovascular events in Study F-153 we identified one fatal adverse event that was adjudicated as non-cardiovascular that may have been misclassified. The subject involved was in the febuxostat 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 proportion of patients with APTC events is 0.3% in the combined febuxostat arms vs. 0.4% in the allopurinol arm. Thus the rate of cardiovascular APTC events was not increased in the febuxostat-treated patients compared with allopurinol-treated patients in Study F-153

Table 20 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. 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.

Table 20: Adjudicated APTC Events in the Long-Term Extension Studies by PY of Exposure

APTC Criterion	Treatment Group				
	Febuxostat				Allopurinol All Doses (N=178) (PY=172.2)
	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 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 21 provides information about adjudicated non-APTC events. 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 21: 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 of cardiovascular events. Cardiovascular risk factors are common in the gout patient population, including hypertension, diabetes, renal impairment 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 22).

Table 22: 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 23 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 23: Subgroup Analysis of Adjudicated APTC Events by Cardiovascular History* in Randomized Controlled Trials

	Febuxostat – all groups		Allopurinol	
	Y	N	Y	N
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 22 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 24 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 rate 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 more frequent with febuxostat than with allopurinol in patients with mild or moderate renal impairment.

Table 24: APTC Events and Renal History in Phase 3 RCTs

Renal disease*	Febuxostat - all groups			Allopurinol		
	normal	mild	moderate	normal	mild	Moderate
FGt06-153	531	816	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.						

It is noted from a pharmacokinetic study conducted in renal impairment subjects (Study TMX-01-008), following the 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 randomized trials. In this type of analysis a relative risk of 1.0 indicates no increased risk. Values above 1.0 indicate an increased risk while values below 1.0 indicate a reduced risk. As shown in Table 25 the relative risk of adjudicated APTC events among febuxostat-treated patients was 2.0 and 2.5 in studies C0-009 and C0-010, respectively. In study F-153, the relative risk was 0.5 for febuxostat. Combining all three Phase 3 trials the relative risk for febuxostat was 1.19. The upper limit of the 95 % confidence interval was 3.8 and the confidence interval included 1.0.

Table 25: 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, 22.1)		(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.

D. 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 evidence of an increased cardiovascular risk.

VI. 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 criteria. These findings suggested that treatment with febuxostat may be associated with a higher risk of cardiovascular events. However, the findings were based on few events and are therefore subject to wide uncertainty.

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 per day 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. In addition, in 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. The FDA is asking the Arthritis Advisory Committee to assess the evidence and provide their assessment of the cardiovascular safety of febuxostat and to assess what dose of febuxostat may provide a favorable risk-benefit relationship.

NDA 21-856 febuxostat
Draft Items for Discussion

1. Safety of febuxostat:

In its review of the two Phase 3 trials of febuxostat 80 mg and 120 mg, the FDA found a larger number of APTC-defined cardiovascular thromboembolic events in the febuxostat arms compared to the active control allopurinol arm. In the subsequent Phase 3 trial of febuxostat 40 mg and 80 mg the event rate for cardiovascular thromboembolic events was not increased with either febuxostat dose compared to the allopurinol control.

Please discuss:

- a. The strength of evidence suggesting a cardiovascular safety signal for the febuxostat 40-mg dose;
- b. The strength of evidence suggesting a cardiovascular safety signal for the febuxostat 80-mg dose

2. Appropriate dosing:

In the two Phase 3 trials of febuxostat 80 mg and 120 mg, the uric acid was decreased more in the febuxostat arms than in the control arm. In the subsequent Phase 3 trial, febuxostat 40 mg met the primary endpoint of non-inferiority to allopurinol. The Applicant has proposed a dose regimen of 40 or 80 mg. Please discuss the efficacy and clinical utility of each dose.

3. Special populations:

For patients with renal impairment it is recommended that the dose of allopurinol be reduced to avoid accumulation of the drug and its metabolites, potentially impairing the ability to achieve target levels of uric acid.

Please discuss:

- a. Whether patients with renal impairment represent an unmet medical need population for uric acid lowering therapies;
- b. The safety, efficacy and clinical utility of febuxostat in patients with renal impairment.

4. In view of the data available for safety and efficacy, discuss the benefit/risk relationship for febuxostat in the treatment of chronic gout.

5. If febuxostat were to be approved, discuss what additional studies should be conducted postapproval to further assess the safety of the product?

6. If febuxostat were not to be approved, discuss what additional studies could be conducted to further assess the cardiovascular risk of febuxostat.

Referenced Articles

1. Abbott, Robert et. al. "Gout and Coronary Heart Disease: The Framingham Study." *J Clin Epidemiol*. Vol 41, No. 3, pp. 237-242, 1988
2. 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.