

Pairwise comparisons were performed only between the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups for the analyses of the Phase 3 controlled studies. Discussions of findings from the febuxostat 240 mg QD, febuxostat 40 mg QD, and placebo treatment groups are included for reference.

7.1.1 Deaths

United States Clinical Program

There were no deaths reported during the single- or multiple-dose **Phase 1** studies

There were total of 8 deaths (6 in ISS and two additional in 4-months SU) reported for subjects taking febuxostat (3 febuxostat 80 mg QD and 5 febuxostat 120 mg QD) in the Phase 2/3 studies (**Table 1**). No deaths were reported in the allopurinol 300/100 mg QD, febuxostat 240 mg QD, febuxostat 40 mg QD, or placebo treatment groups.

Table 1 (Sponsor's Table 2.7k) Deaths in the United States Febuxostat Clinical Program (Phase 2/3 Studies)-ISS

Study No./Phase	Subject/Age/Gender	Adverse Event (MedDRA Preferred Term)	Relationship to Study Drug	Day of Onset ^a	Duration (Days)
Febuxostat 80 mg QD (N=1180)					
C02-010/3	2019/77/Male	Retroperitoneal Hemorrhage	Not Related	287	<1
C02-010/3	2487/65/Male	Respiratory Failure	Not Related	36	175
Febuxostat 120 mg QD (N=876)					
C02-010/3	2403/68/Male	Respiratory Failure	Not Related	170 (6)	7
		Anoxic Encephalopathy	Not Related	171 (7)	6
C02-010/3	2461/74/Male	Colon Cancer Metastatic	Not Related	273	175
C02-021/3	4479/75/Male ^b	Acute Myocardial Infarction	Not Related	12 [203] ^c	Unknown
C02-021/3	2693/60/Male	Myocardial Infarction	Not Related	371 ^d	<1

Phase 2/3 studies included: TMX-00-004, TMX-01-005, C02-009, C02-010, and C02-021.

a Number in parentheses represents the number of days relative to the last dose of study drug.

b Age is listed at time of study entry into C02-021 and day of adverse event onset is from start of C02-021.

c Cumulative days since first dose in C02-009 are shown in brackets.

d Safety data were collected until 30 April 2004 for an interim analysis of Study C02-021; however, this event occurred after 30 April 2004. Cumulative febuxostat exposure was 643 days.

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Table 2 (Sponsor's Table 3.3.a) Deaths in the United States Febuxostat Clinical Program (Phase 2/3 Studies) - 4-Month Safety Update

Study No./ Phase	Subject/Age/ Gender	Adverse Event (MedDRA Preferred Term)	Relationship to Study Drug	Day of Onset of Adverse Event ^a	Duration of Adverse Event (Days)
Febuxostat 80 mg QD (N=1225)					
C02-010/3	2019/77/Female	Retroperitoneal Hemorrhage	Not Related	287	<1
C02-010/3	2487/65/Male	Respiratory Failure	Not Related	56	175
C02-021/3	4387/84/Male ^{b,c}	Sepsis	Not Related	308 (d)	30
Febuxostat 120 mg QD (N=932)					
C02-010/3	2403/68/Male	Respiratory Failure	Not Related	170 (6)	7
		Anoxic Encephalopathy	Not Related	171 (7)	6
C02-010/3	2461/74/Male	Colon Cancer Metastatic	Not Related	273	175
C02-021/3	4479/75/Male ^d	Acute Myocardial Infarction	Not Related	12	Unknown
C02-021/3	2695/60/Male ^e	Myocardial Infarction	Not Related	273 (31)	<1
C02-021/3	4186/84/Female ^{d,e}	Retroperitoneal Hemorrhage ^e	Not Related	432	Unknown

Phase 2/3 studies included: TMX-00-004, TMX-01-005, C02-009, C02-010, and C02-021

a Number in parentheses represents the number of days relative to the last dose of study drug.

b Age is listed at time of study entry into C02-021

c Event occurred after 29 October 2004 cut-off date

d Subject was on allopurinol 300 mg QD in Study C02-009

e New death not previously reported in ISS

Cross-reference: Updated Statistical Tables 7.1.2 and 7.2.2, ISS Appendices 13.3.1 and 13.3.2.3, and Updated Appendices 13.3.1.1.1 and 13.4.2

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Death Narratives

1.

Study C02-021: Febuxostat

Subject 2695

Age: 58

Race: Black

Gender: Male

Significant Medical History: cerebrovascular accident, asthma, congestive heart failure, atrial fibrillation, hypertension, obesity, alcoholism, chronic leg venous insufficiency, hyperventilation syndrome, and renal calculus status post left percutaneous nephrolithotomy

Social History: ex-drinker; ex-tobacco user

Concomitant Medications

(Con Meds):

furosemide, acetylsalicylic acid, digoxin, enalapril, metoprolol succinate, warfarin sodium, and ibuprofen

Study Drug History: C02-010 Dosing:

Day 1-51: febuxostat 80 mg daily (QD)/colchicine 0.6 mg QD

Day 52-371: febuxostat 80 mg QD

C02-021 Dosing:

Day 1-60: febuxostat 120 mg QD/colchicine 0.6 mg QD

Day 61-242: febuxostat 120 mg QD

On Day 273, (cumulative febuxostat exposure: 644 days), the subject had a severe myocardial infarction (MedDRA PT: Myocardial Infarction) resulting in death. The subject was speaking

with his wife at home when he had a massive heart attack. The paramedics were called and they attempted to revive him on the scene without success. He was pronounced dead upon arrival to the hospital. The subject's last confirmed dose of the study drug was on Day 242. Dosing compliance thereafter was unable to be confirmed. The investigator's causality assessment determined that death was not related to the study drug and an alternative etiology of medical history was provided.

2.

Subject 4087

Age: 84

Race: Caucasian

Gender: Male

Significant Medical History: cerebrovascular accident, myocardial infarction, hypertension, coronary bypass surgery, pacemaker insertion, gastroesophageal reflux disease/heartburn, hyperlipidemia, benign prostatic hypertrophy, angina, and hiatal hernia

Social History: 5 alcoholic beverages per week; ex-tobacco user

Concomitant Medications: acetylsalicylic acid, atenolol, ferrous sulfate, finasteride, isosorbide dinitrate, furosemide, glyceryl trinitrate, clopidogrel sulfate, rabeprazole, tamsulosin, lisinopril, simvastatin, erythropoietin, and terazosin hydrochloride

Study Drug History: C02-009 Dosing:

Day -15 to Day -1: colchicine 0.6 mg QD

Day 1-56: febuxostat 80 mg QD/naproxen 250 mg twice a day (BID)

Day 57-196: febuxostat 80 mg QD

C02-021 Dosing:

Day 1-24: febuxostat 80 mg QD/naproxen 250 mg BID

Day 25-27: febuxostat 80 mg QD/naproxen 250 mg BID/indometacin 50 mg three times a day (TID)

Day 28-59: febuxostat 80 mg QD/naproxen 250 mg BID

Day 60-304: febuxostat 80 mg QD

On Day 308 (cumulative febuxostat exposure: 504 days), the subject was hospitalized for repair of a severe worsened hiatal hernia (MedDRA PT: Hiatus Hernia). The subject's last dose of study drug was approximately 3 days earlier in preparation for the planned surgery. The subject experienced a severe, life threatening respiratory arrest (MedDRA PT: Respiratory Arrest) following the surgical procedure. He was resuscitated, intubated, and placed in the intensive care unit. He was also diagnosed with severe sepsis (MedDRA PT: Sepsis) on that day, and at an unspecified time, he also received dialysis. The subject remained hospitalized; however, he was transferred to a second facility. On Day 337, at the request of the family, the subject was removed from the life support system and expired. The death certificate listed the immediate cause of death as sepsis and the underlying causes as hypotension, cholecystitis, and renal insufficiency. The investigator's causality assessment determined that death was not related to the study drug. The investigator provided worsening of medical condition and complication of surgery as the alternative etiologies for the events.

3.

Study C02-010

Subject 2019

Age: 77

Race: Caucasian

Gender: Male

Significant Medical History: angina, congestive heart failure, coronary artery disease, coronary artery bypass graft surgery, pretibial edema, diabetes mellitus, chronic obstructive pulmonary disease, cardiac arrhythmia, and atrial fibrillation

Social History: 1 alcoholic beverage per week; ex-tobacco user

Concomitant Medications:

Events of worsening congestive heart failure/chronic obstructive pulmonary disease: aspirin, Lasix, Diltiazem, Isordil, lisinopril, Digitek, Neurontin, Mirapex, Effexor, Diabeta, and Aciphex

Event of worsening congestive heart failure: Diltiazem, Isordil, Neurontin, Mirapex, Effexor, Aciphex, Zocor, Advair, Micronase, Lanoxin, Lasix, Cardura, Coumadin and colchicine

Event of retroperitoneal hemorrhage: Isordil, Mirapex, Advair, Cardura, aspirin, K-dur, Synthroid, Reglan, Effexor, Micronase, Neurontin, Protonix, Coumadin, Zocor, Lanoxin, Tiazac, Lasix, and colchicine

Study Drug History: Day 1-56: febuxostat 80 mg QD/colchicine 0.6 mg QD

Day 57-287: febuxostat 80 mg QD

On Day 49, the subject was hospitalized for severe worsening of congestive heart failure and severe worsening of chronic obstructive pulmonary disease (MedDRA PTs: Cardiac Failure Congestive and Chronic Obstructive Airways Disease Exacerbated, respectively).

The subject had been experiencing shortness of breath and weakness for 3 weeks prior to hospitalization. Four days prior to his admission he had increasing dyspnea on exertion as well as paroxysmal nocturnal dyspnea. Physical exam on admission revealed mild jugular vein distention, expiratory wheezing in lung fields bilaterally, and bilateral 1+ pitting edema to his knees. A chest x-ray showed pulmonary edema and an electrocardiogram revealed atrial fibrillation at 94 beats/minute. It was decided that the subject was not a good candidate for anticoagulation due to his history of frequent falls. During the hospital course myocardial infarction and deep venous thrombosis were ruled out. Dobutamine thallium scan revealed 1.5 mm of inferior and anterior lateral ST depression, which was considered to be nonspecific secondary to prominent resting changes. A thallium scan, which was limited by the subject's size, showed no obvious scarring and a small inferior area of possible decreased motion.

Echocardiogram revealed an ejection fraction of 60-65% with pulmonary hypertension, moderate regurgitation of the mitral, tricuspid and aortic valves and no wall abnormality. Laboratory tests revealed that the subject's digoxin level was sub therapeutic at less than 0.5 and as a result his digoxin dose was increased.

Other treatments during hospitalization included diuresis with Lasix while maintaining oxygen therapy, initiation of a respiratory protocol and antibiotic therapy. The events resolved on Day 54. The investigator's causality assessment for both events was not related to the study drug and an alternative etiology of pre-existing condition was provided for both events.

On Day 161, the subject was hospitalized for severe worsening of congestive heart failure (MedDRA PT: Cardiac Failure Congestive). The subject developed shortness of breath and was hospitalized. Treatments included Lanoxin and prednisone. The subject's condition improved and the event resolved on Day 163. The study drug was not interrupted due to the event. The investigator's causality assessment was not related to the study drug and an alternative etiology of pre-existing condition was provided.

On Day 287, the subject expired due to a severe retroperitoneal hemorrhage (MedDRA PT: Retroperitoneal Haemorrhage). The subject was receiving prophylaxis anticoagulation therapy with Coumadin due to his history of atrial fibrillation at the time of the event. The subject presented to the emergency room and expired prior to being admitted. The death certificate lists the cause of death as retroperitoneal hemorrhage due to supratherapeutic level on Coumadin therapy as a consequence of chronic atrial fibrillation due to coronary artery disease. The subject was continuing in the study at the time of the event. The date of the last dose of study medication is unknown. The investigator's causality assessment was not related to the study drug and an alternative etiology of Coumadin therapy was provided.

4.

Subject 2403

Age: 68

Race: Caucasian

Gender: Male

Significant Medical History: coronary artery bypass surgery, hyperlipidemia, hypertension, diabetes mellitus, coronary artery disease, and peripheral vascular disease

Social History: non-drinker; ex-tobacco user

Concomitant Medications: Glucotrol XL, Accupril, Avandia, furosemide, Klor-Con, Seroquel, Reminyl, atenolol, and Zocor

Study Drug History: Day 1-59: febuxostat 120 mg QD/colchicine 0.6 mg QD
Day 60-164: febuxostat 120 mg QD

On Day 169, the subject was hospitalized due to severe right carotid stenosis (MedDRA PT: Carotid Artery Stenosis). The subject developed severe short-term memory loss and due to critical stenosis of the right carotid artery he was scheduled for angioplasty and stent placement. The lesion was found to be non-amenable to that procedure and so he underwent carotid endarterectomy. The intraoperative course of the endarterectomy procedure was unremarkable revealing severe right internal carotid artery stenosis.

Postoperatively, he had extreme agitation for which he was kept sedated and treated with Haldol and Ativan but was otherwise stable. On postoperative Day 1, the subject experienced mild asystolic cardiac arrest and severe respiratory failure and anoxic encephalopathy (MedDRA PTs: Cardiac Arrest, Respiratory Failure, and Anoxic Encephalopathy, respectively), which prolonged his hospitalization. The anoxic encephalopathy was also considered to be life threatening by the investigator. After the cardiac arrest the subject was febrile, unresponsive and required ventilator

support. He was placed on antibiotic therapy for possible aspiration pneumonia. Five days later, the subject expired. The death certificate indicated the subject expired due to anoxic encephalopathy as a result of respiratory arrest. Due to the subject's death, compliance cannot be assessed and therefore, the date of the last dose of study medication is unknown. The investigator's causality assessment for all events was not related to the study drug and an alternative etiology of atherosclerosis was provided for the event of carotid stenosis. The alternative etiology for the other events was unknown.

5.

Subject 2461

Age: 74

Race: Caucasian

Gender: Male

Significant Medical History: basal cell carcinoma, and nausea, vomiting and diarrhea related to concurrent colchicine use

Social History: ex-drinker; ex-tobacco user

Concomitant Medications: Synthroid, Zocor, Cordarone, Amaryl, Zestril, aspirin, and Coreg

Study Drug History: Day 1-55: febuxostat 120 mg QD/naproxen 250 mg BID
Day 56-312: febuxostat 120 mg QD

On Day 273, the subject was hospitalized for severe colon cancer with metastasis (MedDRA PT: Colon Cancer Metastatic). The investigator also considered the event to be a persistent or significant disability/incapacity. The subject discontinued the study on Day 313 and eventually expired due to complications of metastatic colon cancer. The subject developed right lower quadrant pain and was initially diagnosed with diverticulitis and treated unsuccessfully with ciprofloxacin. A computed tomography (CT) scan revealed a phlegmon that was suspected to be a peri-appendiceal infection with fistula formation. He underwent surgical exploration, leading to a partial right colectomy with anastomosis, and resection of bowel wall metastasis. A diagnosis of metastatic colon cancer was confirmed. The subject had a mass in the cecum that invaded the lateral abdominal wall and a nodule in the distal ileum, which was a carcinoid tumor. He was discharged from the hospital on hospital Day 8 and was scheduled to begin chemotherapy in 3 weeks. Long-term follow-up information revealed that the subject expired due to colon cancer approximately 4 months after his last dose of study drug. The investigator's causality assessment was not related to the study drug and an alternative etiology of metastasis secondary to colon cancer, cancer due to concurrent illness was provided.

6.

Subject 2487

Age: 65

Race: Black

Gender: Male

Significant Medical History: diabetes mellitus, pneumonia, congestive heart failure, cardiomyopathy, obesity, hyperlipidemia, paroxysmal nocturnal dyspnea, orthopnea, coronary artery disease, angioplasty, myocardial infarction, silent ischemia, transient

renal insufficiency, Darvocet allergy, hypertension and osteoarthritis

Social History: non-drinker; ex-tobacco user

Concomitant Medications: Actos, Zocor, Toprol XL, Glucotrol XL, Coumadin, spironolactone, Atacand, Lasix, and Tylenol Arthritis

Study Drug History: Day 1-13: febuxostat 80 mg QD/colchicine 0.6 mg QD
Day 14-15: febuxostat 80 mg QD/colchicine 0.6 mg BID
Day 16-56: febuxostat 80 mg QD/colchicine 0.6 mg QD
Day 57-64: febuxostat 80 mg QD

On Day 62, the subject was hospitalized due to severe joint pain (MedDRA PT: Arthralgia). Two days prior to hospitalization, the subject complained of pain and was unable to ambulate without assistance. Treatment with Vioxx was started without success and the subject was hospitalized with pain in his knees, ankles, wrists, and right hip. Prior to this event, on or around Day 56, the subject developed non-serious lower extremity edema, hypotension, renal insufficiency, and sepsis, which led to premature discontinuation from the study on Day 65. The subject developed severe serious respiratory failure (MedDRA PT: Respiratory Failure), which prolonged his hospitalization, later became life-threatening and also led to premature discontinuation from the study. On Day 81, the subject developed a severe exacerbation of his congestive heart failure and severe renal failure (MedDRA PTs: Cardiac Failure Congestive and Renal Insufficiency, respectively), both of which prolonged his hospitalization further and were also considered to be life threatening by the investigator. His creatinine levels increased (>5 mg/dL). The subject's respiratory failure worsened; he was intubated and placed on a ventilator. Treatment included fluid hydration and dialysis. The subject remained on a ventilator and died approximately 5 months later. A death certificate was received on _____ . The immediate cause of death was confirmed as respiratory failure as a consequence of sepsis, severe with shock, congestive heart, and coronary artery disease. The investigator's causality assessment was not related to the study drug for all events. The alternative etiologies were joint inflammation for the event of arthralgia, cardiomyopathy for the event of congestive heart failure exacerbation, congestive heart failure for the event of renal failure and renal failure and congestive heart failure for the event of respiratory failure.

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7.

Study C02-021

Subject 4479

Age: 75

Race: Caucasian

Gender: Male

Significant Medical History: hypercholesterolemia, hypertension, coronary artery disease, and dyspnea

Social History: non-drinker; non-tobacco user

Concomitant Medications: aspirin, Zocor, vitamin E, and Motrin

Study Drug History: *C02-009 Dosing:*

Day -1: naproxen 250 mg twice per day (BID)

Day 1-59: febuxostat 240 mg daily (QD)/naproxen 250 mg BID

Day 60-191: febuxostat 240 mg QD

C02-021 Dosing:

Day 1-12: febuxostat 120 mg QD/naproxen 250 mg BID

On Day 12 (cumulative febuxostat exposure: 203 days), the subject expired due to a severe, acute myocardial infarction (MedDRA PT: Acute Myocardial Infarction). The subject was having unknown cardiovascular symptoms and was under the treatment of a cardiologist. A cardiac stress test performed approximately 1 week prior to the subject's death revealed a moderate probability of ischemia. The investigator's causality assessment was not related to the study drug. The investigator provided cardiovascular disease as the alternative etiology for the event.

8.

The death in the subject 4186 (Study C02-021, febuxostat 120 mg QD) occurred after the 29 October 2004 cut-off date and is presented in a CIOMS.

84-year old Caucasian female who died due to a retroperitoneal hemorrhage on Day 432. The subject was initially hospitalized for atrial fibrillation, chronic obstructive pulmonary disease (COPD), and fluid overload. At this time, the subject requested do-not-resuscitate status. She was treated with Lovenox and warfarin, which had to be adjusted, as initial international normalized ratio (INR) values were high. Additional treatments included steroids, furosemide, digoxin, and diltiazem. She was discharged after 9 days of hospitalization with low dose warfarin to be taken every other day. Two days later, she was re-hospitalized for COPD exacerbation. Fourteen days later, the subject developed a retroperitoneal hemorrhage that resulted in her death.

Japan Clinical Program

No deaths occurred following febuxostat administration in the Japan clinical program. As of note, Japan program evaluated lower doses of febuxostat (doses up to 40 mg QD).

Reviewer's comments:

- *For most cases, the possible causal association with the study drug could not be excluded with a possible exception of a death due to metastatic colon CA. Of note, all those patients had multiple pre-existing medical conditions and were on multiple concomitant medications.*
- *Most deaths occurred after 170 days of exposure.*
- *Two subjects had an SAE of retroperitoneal hemorrhage that resulted in death. They were receiving anticoagulation therapy with warfarin due to a history of atrial fibrillation, which caused high INR levels. Of note, in a formal drug interaction study with febuxostat and warfarin in healthy volunteers (Study C03-057) the Sponsor concluded that multiple doses of febuxostat 120 mg QD had no effect on the*

pharmacokinetics or pharmacodynamics (INR and Factor VII) of warfarin. However, 9 (4 in placebo and 5 in febuxostat group) out of 25 subjects in the study experienced increased INR and needed Vit. K therefore they were removed from the study and were not sampled.

- *Two subjects (2487, 2019) experienced CHF exacerbation while on drug.*
- *Patient 4087 died of sepsis however first he suffered life threatening respiratory arrest following surgical procedure for hernia repair and was subsequently died of sepsis*

7.1.2 Other Serious Adverse Events

A serious adverse event was defined as any adverse drug event occurring at any dose that resulted in 1 of the following outcomes: **death, a life-threatening adverse event experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.**

Important medical events that did not result in death, were not life-threatening, or did not require hospitalization could have been considered a serious adverse event when, based upon appropriate medical judgment, they could jeopardize the subject and could require medical or surgical intervention to prevent 1 of the outcomes listed in this definition.

Gout flares were reported as efficacy outcomes. However, 3 gout flares in the Phase 3 controlled studies and 1 after the interim data cutoff in Study C02-021 were reported as SAEs. Each of the gout flare-related SAEs was an exacerbation of the subject's existing gout condition that resulted in inpatient hospitalization.

In the ISS, listings of subjects who experienced an SAE through 10 September 2004 were provided.

The 4-months update Statistical Tables include those SAEs that occurred **until 29 October 2004**. This represents an increase of 30 subjects receiving febuxostat and 5 subjects receiving allopurinol when compared to the ISS. **Of note, the mean exposure in the febuxostat 80 mg QD and febuxostat 120 mg QD group increased by 89 days and 60 days, respectively, while the mean exposure in the allopurinol 300/100 mg QD group increased by 18 days.**

The CIOMS reports were provided for SAEs that occurred after 29 October 2004 but before 31 December 2004. This represents an **additional 10 subjects receiving febuxostat** in Studies TMX-01-005 and C02-021.

Phase 2/3 Studies

The incidence of treatment-emergent serious adverse events in the Phase 2/3 studies in the febuxostat 80 mg QD, febuxostat 120 mg QD, allopurinol 300/100 mg QD, febuxostat 240 mg QD, and febuxostat 40 mg QD treatment groups was 4%, 4%, 5%, 4%, and 4%, respectively and numerically lower in the placebo group (For details, see Sponsor's Table 3.8.2 of ISS).

Table 3 (Sponsor's Table 3.4a) Incidence of Serious Adverse Events (Phase 2/3 Studies)

MedDRA High Level Term MedDRA Preferred Term	Treatment Group n (%)						
	Placebo	Febuxostat					Allopurinol
	(N=172)	All Doses (N=1707)	40 mg QD (N=46)	80 mg QD (N=1180)	120 mg QD (N=876)	240 mg QD (N=134)	300/100 mg QD (N=629)
Treatment-Emergent Serious Adverse Events							
Total Subjects with at Least 1 Adverse Event	2 (1%)	86 (5%)	2 (4%)	42 (4%)	37 (4%)	5 (4%)	29 (5%)
Treatment-Related Serious Adverse Events							
Total Subjects with at Least 1 Adverse Event	0	2 (<1%)	0	1 (<1%)	0	1 (<1%)	0

NEC = not elsewhere classified

Phase 2/3 studies included: TMX-00-004, TMX-01-005, C02-009, C02-010, and C02-021.

Cross-reference: Statistical Tables 3.8.2 and 3.9.2

**Table 4 (Sponsor's Table 3.4.b)
Incidence of Serious Adverse Events (Phase 2/3 Studies) - 4-Month Safety Update**

	Treatment Group n (%)						
	Placebo	Febuxostat					Allopurinol
	(N=172)	All Doses (N=1720)	40 mg QD (N=48)	80 mg QD (N=1225)	120 mg QD (N=932)	240 mg QD (N=134)	300/100 mg QD (N=643)
Treatment-Emergent Serious Adverse Events							
Total Subjects with at Least 1 Serious Adverse Event	2 (1%)	115 (7%)	3 (6%)	65 (5%)	44 (5%)	5 (4%)	34 (5%)
Treatment-Related Serious Adverse Events							
Total Subjects with at Least Serious Adverse Event	0	3 (<1%)	0	2 (<1%)	0	1 (<1%)	0

Studies included: TMX-00-004, TMX-01-005, C02-009, C02-010, and C02-021

Subjects who received study drug from more than 1 dose group are counted in each of those dose groups. Adverse events summarized were reported after the first dose of study drug and within 30 days of last dose of study drug.

Subjects with 1 or more adverse events within a level of MedDRA term are counted only once in that level.

Cross-reference: Updated Statistical Tables 3.8.2 and 3.9.2

For the update, the incidence of treatment-emergent SAEs in the Phase 2/3 studies was 5% (4% in the ISS) in the febuxostat 80 mg QD, 5% (4%) in the febuxostat 120 mg QD and 5% (5%) in the allopurinol treatment groups. In the febuxostat 40 mg QD treatment group, 1 additional subject experienced an SAE. No changes were noted for the placebo and febuxostat 240 mg QD treatment groups as no new data were collected for these 2 groups.

The most frequently occurring serious adverse events in the febuxostat 80 mg QD and 120 mg QD treatment groups included the MedDRA preferred terms cardiac failure congestive, myocardial infarction, atrial fibrillation, and chest pain (Statistical Table 3.8.3).

The most frequently occurring serious adverse events in the allopurinol 300/100 mg QD treatment group included the MedDRA preferred terms coronary artery disease, diverticulitis, and osteoarthritis (Statistical Table 3.8.3).

Table 5 (Sponsor's Table 3.4c, ISS) Incidence of Serious Adverse Events by MedDRA System Organ Class (Phase 3 Controlled Studies)

MedDRA System Organ Class	Placebo (N=134)	Treatment Group n (%)				Allopurinol 300/100 mg QD (N=521)
		All Doses (N=1177)	80 mg QD (N=523)	120 mg QD (N=520)	240 mg QD (N=134)	
Treatment-Emergent Serious Adverse Events						
Total Subjects with at Least 1 Adverse Event	2 (1%)	54 (5%)	21 (4%)	28 (5%)	5 (4%)	25 (5%)
Blood & Lymphatic System Disorders	0	1 (<1%)	0	1 (<1%)	0	0
Cardiac Disorders	1 (<1%)	20 (2%)	10 (2%)	9 (2%)	1 (<1%)	9 (2%)
Gastrointestinal Disorders	0	7 (<1%)	3 (<1%)	2 (<1%)	2 (1%)	3 (<1%)
General Disorders & Administration Site Conditions	0	4 (<1%)	2 (<1%)	2 (<1%)	0	1 (<1%)
Hepatobiliary Disorders	0	0	0	0	0	1 (<1%)
Immune System Disorders	0	1 (<1%)	1 (<1%)	0	0	0
Infections & Infestations	0	6 (<1%)	1 (<1%)	5 (<1%)	0	4 (<1%)
Injury, Poisoning, & Procedural Complications	1 (<1%)	2 (<1%)	2 (<1%)	0	0	0
Investigations	0	1 (<1%)	1 (<1%)	0	0	0
Metabolism & Nutrition Disorders	0	2 (<1%)	0	1 (<1%)	1 (<1%)	0
Musculoskeletal & Connective Tissue Disorders	0	3 (<1%)	3 (<1%)	0	0	3 (<1%)
Neoplasms Benign, Malignant & Unspecified (Incl Cysts & Polyps)	0	5 (<1%)	1 (<1%)	4 (<1%)	0	3 (<1%)
Nervous System Disorders	0	6 (<1%)	1 (<1%)	4 (<1%)	1 (<1%)	1 (<1%)
Renal & Urinary Disorders	0	3 (<1%)	2 (<1%)	0	1 (<1%)	1 (<1%)
Respiratory, Thoracic & Mediastinal Disorders	0	7 (<1%)	5 (<1%)	2 (<1%)	0	0
Vascular Disorders	0	1 (<1%)	0	1 (<1%)	0	0

Phase 3 studies included: C02-019 and C02-019 combined data.
Cross-reference: Statistical Table 3.8.3

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Reviewer's comment:

- It appears there is no difference between treatment groups in the incidence of different SAEs
- However, this summary table is not very informative since it is summarized by MedDRA System Organ Class(SOC) which are very broad categories
- Significant events of interest could be "hidden" within those broad groups

Tables 6, 7 and 8 below provide a line-listing of all SAEs that occurred in the clinical programs.

Table 6 (Sponsor's Table 3.4d, ISS) Other Serious Adverse Events in the United States Febuxostat Clinical Program (Phase 1/2/3 Studies)

Study No./ Phase	Subject/Age/ Gender	Adverse Event (MedDRA Preferred Term)	Relationship to Study Drug	Day of Onset ^a	Duration (Days)	D/C	Comment
Placebo (N=172)							
C02-0093	4345/52/Male	Complications Due to Internal Joint Prosthesis	Not Related	59	49	No	
		Anaemia Postoperative	Not Related	107	92	No	
C02-0093	4508/53/Male	Coronary Artery Disease	Not Related	81 (23)	Ong (230)	No	AE was ongoing as of Study Day in parentheses.
Febuxostat 40 mg QD (N=116)^b							
TMX-01-005/2	1004/56/Male	Appendicitis Perforated	Not Related	330 (11) [356]	3	No	Treatment group is subject's final stable dose & cumulative days since first dose in TMX-00-001 are shown in brackets. AE occurred 11 days after withdrawing from the study. D/C due to AE other than SAE (blood creatinine increased).
TMX-01-005/2	1152/66/Male	Pneumonia	Not Related	586 [614]	5	No	Treatment group is subject's final stable dose & cumulative days since first dose in TMX-00-001 are shown in brackets.
		Cerebrovascular Accident	Not Related	686 [714]	4	No	
		Pneumonia	Not Related	783 [811]	5	No	
Febuxostat 80 mg (N=1180)							
C03-059/1	201/36/Female	Vaginal Laceration	Not Related	7 (6)	19	Yes	Alternative etiology: sexual intercourse

D/C = discontinuation due to the serious adverse event; AE = adverse event; SAE = serious adverse event; Ong = ongoing

a Number in parentheses represents the number of days relative to the last dose of study drug.

b Unique exposures to febuxostat in Phase 1 and Phase 2/3 studies combined.

Cross-reference: Statistical Tables 7.2.1, 7.2.2, 7.3.1, and 7.3.2

Study No./ Phase	Subject/Age/ Gender	Adverse Event (MedDRA Preferred Term)	Relationship to Study Drug	Day of Onset ^a	Duration (Days)	D/C	Comment
Febuxostat 80 mg QD (N=1180) (continued)							
TMX-00-004/2	1043/39/Male	Lobar Pneumonia	Unlikely	23	21	No	Hospitalized for severe pneumonia on Day 23. Onset of Guillain-Barre Syndrome on Day 34 (7 days after last dose). Multiple concomitant medications.
		Delirium Tremens	Unlikely	29 (2)	8	Yes	
		Guillain-Barre Syndrome	Possible	34 (7)	Ong (301)	No	
TMX-01-005/2	1032/74/Female	Rotator Cuff Syndrome	Unlikely	567 [595]	38	No	Treatment group is subject's final stable dose & cumulative days since first dose in TMX-00-001 are shown in brackets.
		Osteoporotic Fracture	Not Related	669 [697]	19	No	
		Excoriation	Not Related	842 [870]	Ong (897)	No	
TMX-01-005/2	1042/75/Male	Chest Pain	Not Related	27 [56]	10	Yes	Treatment group is subject's final stable dose & cumulative days since first dose in TMX-00-001 are shown in brackets. Atrial fibrillation occurred 8 days after withdrawing from the study and D/C due to AEs other than SAE (referral to cardiac catheterization laboratory). Subject was also receiving colchicine at time of event.
		Atrial Fibrillation	Not Related	35 (8) [64]	Ong (180)	No	
TMX-01-005/2	1047/55/Male	Cholecystitis	Unlikely	336 [383]	6	No	Treatment group is subject's final stable dose & cumulative days since first dose in TMX-00-001 are shown in brackets.

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 NDA 21-856
 Febuxostat (Uloric)

Study No./Phase	Subject/Age/Gender	Adverse Event (MedDRA Preferred Term)	Relationship to Study Drug	Day of Onset*	Duration (Days)	D/C	Comment
Febuxostat 80 mg QD (N=1180) (continued)							
TMX-01-005/2	1052/70/Female	Dementia Alzheimer's Type	Not Related	104 [132]	8	Yes	Treatment group is subject's final stable dose & cumulative days since first dose in TMX-00-004 are shown in brackets.
TMX-01-005/2	1092/52/Male	Atrial Fibrillation	Not Related	812 [870]	<1	No	Treatment group is subject's final stable dose & cumulative days since first dose in TMX-00-004 are shown in brackets.
TMX-01-005/2	1163/64/Male	Diverticular Perforation	Not Related	613 [641]	3	No	Treatment group is subject's final stable dose & cumulative days since first dose in TMX-00-004 are shown in brackets.
TMX-01-005/2	1122/75/Male	Benign Lung Neoplasm	Unlikely	327 [356]	53	No	Treatment group is subject's final stable dose & cumulative days since first dose in TMX-00-004 are shown in brackets.
TMX-01-005/2	1177/56/Male	Tongue Neoplasm Malignant Stage Unspecified	Not Related	269 [295]	Ong (345)	Yes	Treatment group is subject's final stable dose & cumulative days since first dose in TMX-00-004 are shown in brackets.
C02-009/3	4240/51/Male	Chest Pain	Unlikely	50	2	No	
Febuxostat 80 mg QD (N=1180) (continued)							
C02-009/3	4504/66/Male	Prostate Cancer	Unlikely	64 (3)	Ong (64)	No	AE was ongoing as of Study Day in parentheses.
C02-009/3	4478/31/Male	Implantable Defibrillator Malfunction	Not Related	189	<1	No	
C02-009/3	4630/48/Male	Chest Pain	Not Related	126	4	No	
C02-009/3	4666/68/Female	Abdominal Pain	Not Related	162	17	No	
C02-009/3	4670/64/Female	Chronic Obstructive Airways Disease Exacerbated	Unlikely	15	6	No	
C02-009/3		Coronary Artery Atherosclerosis	Not Related	53	3	No	
C02-009/3	4773/65/Male	Transient Ischemic Attack	Not Related	60	<1	No	
C02-009/3	4813/49/Male	Coronary Artery Disease	Not Related	149	Ong (295)	Yes	AE was ongoing as of Study Day in parentheses.
C02-009/3	4858/50/Male	Pleuritic Pain	Not Related	78 (2)	13	Yes	
C02-009/3	6007/48/Male	Myocardial Infarction	Unlikely	99	11	No	
C02-009/3	6014/68/Female	Nausea	Unlikely	95 (1)	13	Yes	
		Muscular Weakness	Unlikely	95 (1)	144	Yes	
		Vomiting	Unlikely	95 (1)	13	Yes	
C02-010/3	2019/77/Male	Cardiac Failure Congestive	Not Related	49	6	No	LVC due to SAE other than these SAEs (expired due to retroperitoneal haemorrhage).
		Chronic Obstructive Airways Disease Exacerbated	Not Related	49	6	No	
		Cardiac Failure Congestive	Not Related	161	3	No	
C02-010/3	2020/77/Male	Cardiac Failure Congestive	Not Related	248	46	No	
		Renal Failure Acute International Normalised Ratio Increased	Not Related	248	46	No	
		Renal Failure Acute International Normalised Ratio Increased	Not Related	272	22	No	
		Abscess	Not Related	277	82	No	

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Tatiana Oussova, MD
NDA 21-856
Febuxostat (Uloric)

Study No./Phase	Subject/Age/Gender	Adverse Event (MedDRA Preferred Term)	Relationship to Study Drug	Day of Onset*	Duration (Days)	D/C	Comment
Febuxostat 80 mg OD (N=1190) (continued)							
C02-010/3	2158/60/Male	Atrial Fibrillation	Not Related	49	2	No	
		Atrial Fibrillation	Not Related	344	3	No	
C02-010/3	2334/60/Male	Myocardial Infarction	Not Related	166	<1	No	
C02-010/3	2356/37/Male	Angina Pectoris	Not Related	195	3	No	
C02-010/3	2432/32/Male	Overdose	Not Related	78 (49)	21	Yes	AE was secondary reason for premature D/C (lost to follow-up was primary reason) and overdose drug not documented. Event occurred posttreatment, however, the last day of dosing was estimated, as this information was unavailable.
C02-010/3	2487/63/Male	Arthralgia	Not Related	62	169	No	Subject was hospitalized due to SAE and unable to return study drug. Expired due to respiratory failure. D/C also due to other AEs (oedema peripheral, hypotension, and sepsis).
		Cardiac Failure Congestive	Not Related	81 (17)	150	Yes	
		Renal Insufficiency	Not Related	81 (17)	150	Yes	
C02-010/3	2611/66/Male	Spinal Column Stenosis	Not Related	266 (1)	Ong (323)	No	AE was ongoing as of Study Day in parentheses.
C02-010/3	2644/49/Male	Drug Hypersensitivity	Not Related	306	10	Yes	
Febuxostat 80 mg OD (N=1190) (continued)							
C02-010/3	2745/41/Male	Road Traffic Accident	Not Related	167 (20)	45	Yes	Event occurred posttreatment, however, the last day of dosing was estimated, as this information was unavailable.
		Head Injury	Not Related	167 (20)	45	Yes	
		Haemothorax	Not Related	167 (20)	45	Yes	
		Pneumothorax	Not Related	167 (20)	45	Yes	
C02-010/3	2764/42/Male	Angina Pectoris	Not Related	231	Unknown	No	
C02-021/3	3004/64/Male	Myocardial Infarction	Not Related	138 [502]	5	No	Age at time of study entry for Study C02-010. AE onset day is from start of C02-021. Cumulative days since first dose in C02-010 are shown in brackets.
		Ventricle Rupture	Not Related	143 [507]	10	No	
C02-021/3	2963/68/Male	Coronary Artery Disease	Not Related	75 [450]	6	No	Age at time of study entry for Study C02-010. AE onset day is from start of C02-021. Cumulative days since first dose in C02-010 are shown in brackets.
C02-021/3	2127/65/Male	Rotator Cuff Syndrome	Not Related	5 [355]	101	No	Age at time of study entry for Study C02-010. AE onset day is from start of C02-021. Cumulative days since first dose in C02-010 are shown in brackets.

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NDA 21-856
Febuxostat (Uloric)

Study No./Phase	Subject/Age/Gender	Adverse Event (MedDRA Preferred Term)	Relationship to Study Drug	Day of Onset*	Duration (Days)	D/C	Comment
Febuxostat 80 mg QD (N=1180) (continued)							
C02-021/3	2165/47/Male	Asthma	Not Related	139 [503]	19	No	Age at time of study entry for Study C02-010. AE onset day is from start of C02-021. Cumulative days since first dose in C02-010 are shown in brackets.
C02-021/3	2376/79/Male	Pneumonia Endocarditis	Not Related Not Related	51 [415] 162 [526]	7 32	No No	Age at time of study entry for Study C02-010. AE onset day is from start of C02-021. Cumulative days since first dose in C02-010 are shown in brackets.
C02-021/3	2459/48/Male	Hepatitis Acute	Not Related	28 [390]	Ong (70)	Yes	Age at time of study entry for Study C02-010. AE onset day is from start of C02-021. AE was ongoing as of day in parentheses. Cumulative days since first dose in C02-010 are shown in brackets.
C02-021/3	2606/49/Male	Hypertension	Unlikely	105 [468]	36	No	Age at time of study entry for Study C02-010. AE onset day is from start of C02-021. Cumulative days since first dose in C02-010 are shown in brackets.
C02-021/3	2736/73/Male	Staphylococcal Infection	Not Related	56 [426]	6	No	Age at time of study entry for Study C02-010. AE onset day is from start of C02-021. Cumulative days since first dose in C02-010 are shown in brackets.

Study No./Phase	Subject/Age/Gender	Adverse Event (MedDRA Preferred Term)	Relationship to Study Drug	Day of Onset*	Duration (Days)	D/C	Comment
Febuxostat 80 mg QD (N=1180) (continued)							
C02-021/3	4056/71/Male	Coronary Artery Occlusion	Not Related	176 [371]	2	No	Age at time of study entry for Study C02-009. AE onset day is from start of C02-021. Cumulative days since first dose in C02-009 are shown in brackets.
C02-021/3	4095/55/Male	Chest Pain	Not Related	57 [253]	2	No	Age at time of study entry for Study C02-009. AE onset day is from start of C02-021. Cumulative days since first dose in C02-009 are shown in brackets.
C02-021/3	4222/49/Male	Localised Osteoarthritis	Not Related	4 [193]	3	No	Age at time of study entry for Study C02-009. AE onset day is from start of C02-021. Cumulative days since first dose in C02-009 are shown in brackets.
C02-021/3	4959/71/Male	Pneumonia Cardiac Failure Congestive	Not Related Not Related	13 [215] 13 [215]	3 3	No No	Age at time of study entry for Study C02-009. AE onset day is from start of C02-021. Cumulative days since first dose in C02-009 are shown in brackets.

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 NDA 21-856
 Febuxostat (Uloric)

Study No./Phase	Subject/Age/Gender	Adverse Event (MedDRA Preferred Term)	Relationship to Study Drug	Day of Onset*	Duration (Days)	D/C	Comment
Febuxostat 120 mg QD (N=876)							
TMX-00-004/2	1136/55/Male	Back Pain	Not Related	12	3	No	
TMX-00-004/2	1043/54/Female	Suicide Attempt	Unlikely	21	6	Yes	
TMX-01-005/2	1164/46/Male	Traumatic Fracture Concussion	Not Related Not Related	121 [150] 121 [150]	<1 <1	No No	Treatment group is subject's final stable dose & cumulative days since first dose in TMX-00-004 are shown in brackets.
TMX-01-005/2	1180/78/Male	Basal Cell Carcinoma	Unlikely	77 [103]	32	No	Treatment group is subject's final stable dose & cumulative days since first dose in TMX-00-004 are shown in brackets. D/C due to AE other than SAE (rectal haemorrhage).
C02-009/3	4092/51/Male	Chest Pain	Not Related	93	3	No	D/C from Study C02-021 due to AE other than SAE (blood creatinine increased).
C02-009/3	4308/68/Male	Atrial Fibrillation	Unlikely	127	7	No	
C02-009/3	4371/47/Male	Acute Coronary Syndrome	Unlikely	61 (1)	2	Yes	
C02-009/3	4470/55/Male	Myocardial Infarction	Unlikely	64	6	Yes	
C02-009/3	4551/50/Male	Anaemia	Unlikely	47	30	Yes	
C02-009/3	4633/73/Male	Cardiomyopathy	Not Related	72 (2)	101	No	
C02-009/3	4665/75/Male	Hypoglycaemic Seizure	Not Related	21	8	Yes	
Febuxostat 120 mg QD (N=876) (continued)							
C02-009/3	4819/65/Male	Parathyroid Tumour Malignant	Not Related	39	55	Yes	
C02-009/3	5033/47/Male	Colon Cancer Metastatic	Not Related	196 (4)	Ong (270)	No	AE was ongoing as of Study Day in parentheses.
C02-010/3	2040/63/Male	Prostate Cancer	Not Related	270	Ong (605)	Yes	AE was ongoing as of Study Day in parentheses.
C02-010/3	2125/74/Male	Gastroenteritis Viral	Not Related	194	17	No	
C02-010/3	2198/52/Female	Cellulitis	Not Related	15	2	No	
C02-010/3	2201/63/Male	Cerebrovascular Accident	Unlikely	30 (29)	7	Yes	Event occurred posttreatment; however, the last day of dosing was estimated, as this information was unavailable.
C02-010/3	2223/51/Male	Myocardial Infarction	Unlikely	313	1	Yes	
C02-010/3	2244/42/Male	Deep Vein Thrombosis	Not Related	15	4	No	
Febuxostat 120 mg QD (N=876) (continued)							
C02-010/3	2382/55/Male	Pulmonary Embolism	Unlikely	197 (15)	Ong (211)	No	Event occurred posttreatment; however, the last day of dosing was estimated, as this information was unavailable. AE was ongoing as of Study Day in parentheses.
C02-010/3	2403/68/Male	Carotid Artery Stenosis Cardiac Arrest	Not Related Not Related	169 (5) 171 (7)	8 6	Yes No	Subject expired due to respiratory failure and anoxic encephalopathy.
C02-010/3	2426/58/Male	Rectal Hemorrhage Pancreatitis Chronic	Unlikely Unlikely	221 224	4 9	No No	
C02-010/3	2433/65/Male	Cardiac Arrest Pneumonia Acute Myocardial Infarction	Not Related Not Related Not Related	311 311 311	Unknown 5 5	No No No	
C02-010/3	2504/32/Male	Appendicitis Perforated	Unlikely	321	51	No	
C02-010/3	2553/42/Male	Diverticulitis	Not Related	3	4	Yes	
C02-010/3	2618/62/Male	Atrial Fibrillation	Not Related	317	4	No	
C02-010/3	2658/66/Female	Syncope	Not Related	260	4	No	
C02-010/3	2698/69/Male	Urinary Tract Infection Benign Prostatic Hyperplasia	Not Related Not Related	133 (1) 167 (35)	9 3	No No	
C02-010/3	2697/60/Male	Cervical Myelopathy	Not Related	239	4	No	
C02-010/3	2775/69/Male	Paresthesia	Not Related	109	8	Yes	

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Study No./ Phase	Subject/Age/ Gender	Adverse Event (MedDRA Preferred Term)	Relationship to Study Drug	Day of Onset ^a	Duration (Days)	D/C	Comment
Febuxostat 120 mg QD (N=876) (continued)							
C02-010/3	2865/52/Male	Cardiac Failure Congestive	Not Related	51	7	No	
		Cardiac Failure Congestive	Not Related	211	4	No	
C02-021/3	2610/62/Male	Localised Osteoarthritis	Not Related	63 [420]	<1	No	Age at time of study entry for Study C02-010. AE onset day is from start of C02-021. Cumulative days since first dose in C02-010 are shown in brackets.
C02-021/3	2779/40/Male	Myocardial Infarction	Unlikely	44 [405]	2	No	Age at time of study entry for Study C02-010. AE onset day is from start of C02-021. Cumulative days since first dose in C02-010 are shown in brackets.
C02-021/3	4057/60/Male	Ischaemic Stroke	Unlikely	106 [301]	15	No	Age at time of study entry for Study C02-009. AE onset day is from start of C02-021. Cumulative days since first dose in C02-009 are shown in brackets.
		Cardiac Failure Congestive	Not Related	169 [364]	5	No	
Febuxostat 120 mg QD (N=876) (continued)							
C02-021/3	4059/68/Male	Bronchiectasis	Not Related	142 [337]	7	No	Age at time of study entry for Study C02-009. AE onset day is from start of C02-021. Cumulative days since first dose in C02-009 are shown in brackets.
		Pneumonia	Not Related	175 [370]	7	No	
C02-021/3	4175/65/Male	Cardiac Failure Congestive	Unlikely	39 [256]	33	No	Age at time of study entry for Study C02-009. AE onset day is from start of C02-021. Cumulative days since first dose in C02-009 are shown in brackets.
Febuxostat 240 mg QD (N=134)							
C02-009/3	4067/71/Male	Small Intestinal Obstruction	Not Related	69	10	No	
		Convulsion	Not Related	168 (1)	3	No	
C02-009/3	4518/79/Male	Hypovolaemia	Unlikely	133 (3)	5	No	D/C due to AE other than SAE (gastroenteritis).
C02-009/3	4650/40/Male	Renal Impairment	Probable	197 (1)	97	No	Event considered medically important by investigator. Serum creatinine was 1.5 mg/dL on Day -5. Maximum creatinine during treatment was also 1.5 mg/dL.
C02-009/3	4850/56/Female	Supraventricular Tachycardia	Unlikely	108	4	No	
C02-009/3	4894/61/Male	Abdominal Strangulated Hernia	Not Related	176	5	No	
Aleparinol 300/100 mg QD (N=629)							
C02-009/3	4009/61/Male	Cholelithiasis	Not Related	139	2	No	
C02-009/3	4027/41/Male	Primary Tumour Benign	Unlikely	121 (21)	38	No	

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 NDA 21-856
 Febuxostat (Uloric)

Study No./Phase	Subject/Age/Gender	Adverse Event (MedDRA Preferred Term)	Relationship to Study Drug	Day of Onset ^a	Duration (Days)	D/C	Comment
Allopurinol 300/100 mg QD (N=629) (continued)							
C02-009/3	4161/54/Male	Appendicitis Perforated	Not Related	127	9	No	
C02-009/3	4528/66/Female	Hodgkin's Disease	Not Related	56 (1)	245	Yes	
C02-009/3	4753/52/Male	Gastroenteritis	Not Related	123	3	No	
C02-009/3	4761/66/Male	Chest Pain	Not Related	34	<1	No	
C02-009/3	4778/67/Male	Osteoarthritis	Not Related	182	5	No	
C02-010/3	2068/48/Male	Coronary Artery Disease	Not Related	6	2	No	D/C due to AE other than SAE (abdominal pain lower).
C02-010/3	2111/53/Male	Back Pain	Not Related	5 (4)	8	No	D/C due to AE other than SAE (abdominal pain lower).
C02-010/3	2193/37/Male	Staphylococcal Infection	Not Related	162	6	No	
C02-010/3	2199/63/Male	Coronary Artery Disease	Not Related	112	3	No	
C02-010/3	2247/49/Male	Testicular Germ Cell Cancer	Not Related	359	Unknown	No	
C02-010/3	2315/56/Male	Syncope	Unlikely	37	Unknown	No	
C02-010/3	2318/39/Male	Nephrolithiasis	Unlikely	9	9	No	
C02-010/3	2361/41/Male	Diverticulitis	Not Related	82	10	No	
C02-010/3	2384/78/Male	Umbilical Hernia	Not Related	36	3	No	
C02-010/3	3486/63/Female	Cardiovascular Disorder	Not Related	9 (8)	40	No	
C02-010/3	2499/88/Male	Coronary Artery Occlusion	Not Related	266	2	No	
C02-010/3	2559/68/Male	Coronary Artery Disease	Not Related	65	2	No	
C02-010/3	2565/62/Male	Myocardial Infarction	Not Related	207	7	No	
C02-010/3	2572/55/Male	Diverticulitis	Not Related	267	27	No	
		Enterovesical Fistula	Not Related	267	27	No	
		Diverticular Perforation	Not Related	267	27	No	
C02-010/3	2584/56/Male	Angina Pectoris	Not Related	214	2	No	
C02-010/3	2612/64/Male	Osteoarthritis	Not Related	153	11	No	
Allopurinol 300/100 mg QD (N=629) (continued)							
C02-010/3	2686/67/Male	Ventricular Extrasystoles	Not Related	171	Ong (495)	No	AE was ongoing as of Study Day in parentheses.
C02-010/3	2817/79/Female	Bradycardia	Unlikely	94	2	Yes	
C02-021/3	2575/53/Male	Optic Neuritis Retrobulbar	Unlikely	36 [412]	Ong (184)	Yes	Age at time of study entry for Study C02-010. AE onset day is from start of C02-021. AE was ongoing as of Study Day in parentheses. Cumulative days since first dose in C02-010 are shown in brackets.
C02-021/3	2697/60/Male	Small Intestinal Perforation	Not Related	122 [484]	3	No	Age at time of study entry for Study C02-010. AE onset day is from start of C02-021. Cumulative days since first dose in C02-010 are shown in brackets.
C02-021/3	4308/68/Male	Cardiac Failure Congestive	Not Related	104 [295]	5	No	Age at time of study entry for Study C02-009. AE onset day is from start of C02-021. Cumulative days since first dose in C02-009 are shown in brackets.
C02-021/3	4770/45/Male	Cervical Spinal Stenosis	Not Related	12 [207]	2	No	Age at time of study entry for Study C02-009. AE onset day is from start of C02-021. Cumulative days since first dose in C02-009 are shown in brackets.
		Intervertebral Disc Disorder	Not Related	12 [207]	2	No	

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An additional 30 subjects (27 febuxostat, 3 allopurinol) in Studies TMX-01-005 and C02-021 experienced serious adverse events that occurred after this cut-off date and are listed in Table 7.

Table 7 (Sponsor's Table 3.4e, ISS) Serious Adverse Events (Initial Reports) Occurring in Studies TMX-01-005 (from 16 September 2003 to 10 September 2004) and C02-021 (from 1 May 2004 to 10 September 2004)

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 Tatiana Oussova, MD
 NDA 21-856
 Febuxostat (Uloric)

Study No./Phase	Subject/Age/Gender	Adverse Event (MedDRA Preferred Term)	Relationship to Study Drug	Day of Onset ^a	Duration (Days)	D/C	Comment
Febuxostat 40 mg QD							
TMX-01-005/2	1152/68/Male	Lumbar Spinal Stenosis	Not Related	1096 [1096]	Unknown	No	Subject also experienced an SAE within the cut-off date for Study TMX-01-005.
Febuxostat 80 mg QD							
C02-021/3	4263/65/Male	Myocardial Infarction	Not Related	82 [281]	Unknown	No	
C02-021/3	4398/50/Male	Idiopathic Thrombocytopenic Purpura	Probable	116 [238] ^c	Unknown	Yes	In vitro platelet aggregation and activation studies revealed that febuxostat-treated serum did not induce platelet aggregation or cause significant platelet activation.
C02-021/3	4894/62/Male	Cholelithiasis	Not Related	22 [217]	Unknown ^b	No	Subject also experienced an SAE in Study C02-009.
C02-021/3	4963/81/Female	Myocardial Infarction	Not Related	83 [278]	Unknown	No	
C02-021/3	2619/63/Male	Localized Osteoarthritis	Not Related	205 [562]	Unknown	No	
C02-021/3	4641/50/Male	Cardiac Stress Test Abnormal	Unlikely	84 [84]	Unknown	No	
		Renal Failure Acute	Not Related	118 [118]	Unknown	No	

D/C = discontinuation; AE = adverse event; SAE = serious adverse event; Ong = ongoing

a Cumulative febuxostat days are shown in brackets.

b Subject received 196 days of febuxostat 80 mg QD in Study C02-009. In Study C02-021, the subject received 70 days of allopurinol and then switched to receive 42 days of febuxostat 80 mg QD.

c Adverse event resolved; duration not provided.

Cross-reference: TAP Pharmacovigilance Database

Study No./Phase	Subject/Age/Gender	Adverse Event (MedDRA Preferred Term)	Relationship to Study Drug	Day of Onset	Duration (Days)	D/C	Comment
Febuxostat 80 mg QD (continued)							
C02-021/3	2820/60/Male	Enteritis Infections	Not Related	158 [158]	Ongoing	No	
C02-021/3	4144/63/Male	Pituitary Tumour	Unlikely	208 [208]	Ongoing	No	
C02-021/3	2736/75/Male	Benign Neoplasm	Not Related	187 [187]	Unknown ^a	No	Subject also experienced an SAE within the cut-off date for Study C02-021.
C02-021/3	6022/66/Male	Cholecystitis	Not Related	164 [164]	Unknown ^a	No	
C02-021/3	2002/79/Male	Aortic Aneurysm	Unlikely	367 [367]	Ongoing	Unknown	
C02-021/3	2276/70/Male	Cerebellar Infarction	Not Related	302 [672]	Ongoing	No	

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Study No./Phase	Subject/Age/Gender	Adverse Event (MedDRA Preferred Term)	Relationship to Study Drug	Day of Onset	Duration (Days)	D/C	Comment
Febuxostat 80 mg QD (continued)							
C02-021/3	4029/50/Male	Coronary Artery Stenosis	Unlikely	19 [223]	Unknown ^a	No	
C02-021/3	2686/38/Male	Coronary Artery Diseases	Not Related	118 [118]	Unknown ^a	No	Subject also experienced an SAE in Study C02-010.
TMX-01-005/2	1100/37/Male	Atrial Fibrillation	Unlikely	1074 [1102]	Unknown	No	
TMX-01-005/2	1118/47/Male	Depression	Not Related	1058 [1087]	Unknown	No	
TMX-01-005/2	1122/38/Male	Arrhythmia Pneumonia	Not Related Not Related	1136 [1165] 937 [976]	Unknown ^a Unknown ^a	No No	Subject also experienced an SAE within the cut-off date for Study TMX-01-005.
TMX-01-005/2	1165/32/Female	Diverticulitis	Not Related	852 [880]	2	No	
Febuxostat 120 mg QD							
C02-021/3	2198/52/Female	Chest Pain	Not Related	201 [572]	Unknown ^a	No	Subject also experienced an SAE in Study C02-010.
Febuxostat 120 mg QD (continued)							
C02-021/3	2789/52/Male	Chest Pain	Not Related	124 [493]	Unknown	No	
C02-021/3	4163/55/Female	Ovarian Cyst	Unlikely	Unknown	Unknown ^a	Yes	
C02-021/3	2521/41/Male	Alcoholism	Not Related	266 [580]	2	No	AE did not result in hospitalization and was down graded to a non-serious AE on September 13, 2004
C02-021/3	2221/46/Male	Intestinal Obstruction	Unlikely	194 [562]	2	No	
C02-021/3	2426/39/Male	Obesity	Not Related	181 [559]	Unknown ^a	No	Subject also experienced an SAE in Study C02-010.
Febuxostat 120 mg QD (continued)							
C02-021/3	4329/31/Male	Myocardial Infarction	Not Related	27 [27]	Unknown	No	
C02-021/3	4744/69/Male	Syncope	Possible	176 [176]	Ongoing	No	
Allopurinol 300 mg QD							
C02-021/3	4674/61/Male	Chest Pain	Unlikely	84 [203]	Unknown	No	Febuxostat days in C02-009 are shown in brackets.
C02-021/3	2543/69/Male	Diverticulitis	Unlikely	147 [365]	Unknown ^a	No	Febuxostat days in C02-010 are shown in brackets.
C02-021/3	4484/56/Male	Appendicitis	Not Related	192	Unknown ^a	Yes	

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A total of 11 febuxostat subjects experienced treatment-emergent serious adverse events in the Japan clinical program, including 9 in the Phase 2 open-label, long-term study of febuxostat (TMX-67-11) and 1 each in the Phase 3 double-blind studies (TMX-67-12 and TMX-67-13). All subjects with treatment-emergent serious adverse events were hospitalized. The majority of serious adverse events occurred after 6 months of treatment and resolved within 2 months.

Table 8 (Sponsor's Table 3.4f, ISS) Serious Adverse Events Reported in Japan Clinical Studies

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 Febuxostat (Uloric)

Study Number/ Phase	Subject Number	MedDRA Preferred Term/Reported Term	Relationship to Study Drug	Day of Onset	Duration (Days)
Febuxostat 10 mg QD					
TMX-67-11/2	52-045	Stomach Discomfort/Stomach Discomfort ^a	Not Related	173	Unknown
TMX-67-11/2	28-162	Upper Respiratory Tract Inflammation/ Acute Upper Respiratory Tract Inflammation	Not Related	84	20
TMX-67-11/2	52-085	Dysstasia/Difficulty in Standing	Not Related	271	2
Febuxostat 10 - 20 mg QD					
TMX-67-11/2	52-073	Cholestasis/Cholestatic Hepatic Disorder Gamma Glutamyltransferase Increased/ Gamma-GTP Increased	Not Related	230	49
TMX-67-11/2	28-054	Putamen Haemorrhage/Left Putamen Haemorrhage	Not Related	161	64
Febuxostat 10 - 40 mg QD					
TMX-67-11/2	28-075	Joint Ligament Rupture/ Anterior Cruciate Ligament Disruption of Right Knee	Not Related	173	Unknown
TMX-67-11/2	52-003	Arthropathy/ Ache in Left Knee (Left Gonarthrosis Aggravated)	Not Related	315	21
TMX-67-11/2	52-063	Tendon Rupture/Left Achilles Tendon Rupture	Not Related	253	87
TMX-67-11/2	28-126	Tonsillitis/Tonsillitis ^a	Not Related	120	8
TMX-67-12/3	005-B	Pain in Extremity/Pain from Left Back Thigh to Left Knee Joint	Not Related	14	3
TMX-67-13/3	023-B	Gouty Arthritis/Gout Flare in Left Leg Joint	Not Related	49	Unknown

NOS = not otherwise specified

a Subject prematurely discontinued study drug due to this adverse event.

Note: Subject numbers reflect those assigned by Teijin in the clinical study, whereas those in the CIOMS were generated by the investigator.

Cross-reference: TMX-67-11, TMX-67-12, and TMX-67-13 CSRs

A listing of all subjects who experienced other serious adverse event (other than those resulting in death) in Studies TMX-01-005 and C02-021 between 10 September 2004 and 29 October 2004 is provided in Table 9, and a listing of subjects who experienced other serious adverse event (other than those resulting in death) in these studies from 29 October 2004 through 31 December 2004 is provided in Table 10. The majority of SAEs began after the subject had been treated with study drug for at least 3 months and most resolved within 2 weeks of onset.

Table 9 (Sponsor's Table 3.4.c of SU) Other Serious Adverse Events Reported in Studies TMX-01-005 and C02-021 from 10 September 2004 through 29 October 2004

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Study No./ Phase	Subject/Age/ Gender	Adverse Event (MedDRA Preferred Term)	Relationship to Study Drug	Day of Onset ^a	Duration (Days) ^b	D/C	Comment
Febuxostat 40 mg QD (N=116^c)							
TMX-01-005/2	1118/64/Male	Depression	Not Related	1058 [1087]	5	No	Alternate Etiology: Stress or Lexapro
TMX-01-005/2	1152/66/Male	Pneumonia ^d	Not Related	586 [614]	5	No	Alternate Etiology: Spondylosis
		Cerebrovascular Accident ^d	Not Related	686 [714]	4	No	
		Pneumonia ^d	Not Related	783 [811]	5	No	
		Lumbar Spinal Stenosis ^e	Not Related	1097 [1125]	3	No	
Febuxostat 80 mg (N=167^d)							
TMX-01-005/2	1055/49/Male	Prostate Cancer	Unlikely	1231 [1258]	Ong (1312)	Yes	Alternate Etiology: Genetic predisposition
TMX-01-005/2	1100/34/Male	Atrial Fibrillation ^e	Unlikely	1074 [1102]	123	No	Alternate Etiology: Possible acute coronary syndrome
TMX-01-005/2	1122/75/Male	Benign Lung Neoplasm ^f	Unlikely	327 [356]	53	No	Alternate Etiology: Probable old pulmonary etiology, bacterial, history of Heart Disease
		Pneumonia ^g	Not Related	948 [977]	5	No	
		Atrioventricular Block Second Degree	Not Related	1075 [1102]	6	No	
TMX-01-005/2	1165/69/Female	Diverticulitis ^h	Not Related	852 [880]	3	No	Alternate Etiology: Bacterial infection, abdominal adhesion
		Small Intestinal Obstruction	Not Related	1210 [1238]	3	No	

D/C = discontinuation due to the serious adverse event; AE = adverse event; SAE = serious adverse event; Ong = ongoing

^a Number in brackets represents the cumulative study days since the first dose of study drug

^b AE was ongoing as of Study Day in parentheses

^c Unique exposures to febuxostat in Phase 1 and Phase 2/3 studies combined

^d Event previously reported in the ISS

^e Event previously reported in the ISS; updated information

Note: Treatment group is subject's final stable dose

Cross-reference: Updated Statistical Tables 7.2.2, 7.3.2 and TAP Pharmacovigilance database

Study No./ Phase	Subject/Age/ Gender	Adverse Event (MedDRA Preferred Term)	Relationship to Study Drug	Day of Onset ^a	Duration (Days) ^b	D/C	Comment
Febuxostat 80 mg (N=167^d)							
C02-021/3	2002/77/Male	Aortic Aneurism	Not Related	367 [734]	40	No	Alternate Etiology: Blood vessel weakening
C02-021/3	2270/68/Male	Brain Stem Infarction ^e	Not Related	302 [672]	4	No	Alternate Etiology: Ischemia
C02-021/3	2676/61/Male	B-cell Lymphoma	Not Related	270 [633]	Ong (302)	Yes	
C02-021/3	2686/67/Male	Coronary Artery Disease ^e	Not Related	245 [609]	13	No	Alternate Etiology: Cholesterol deposition
C02-021/3	2736/73/Male	Staphylococcal Infection ^g	Not Related	56 [426]	6	No	Alternate Etiology: Spontaneous. AE onset day is from start of C02-021.
		Benign Neoplasm	Not Related	184 [554]	5	Yes	
C02-021/3	2820/58/Male	Diverticulitis ^h	Not Related	159 [530]	9	No	Alternate Etiology: Diverticulitis
C02-021/3	2852/52/Male	Diverticulitis	Not Related	250 [610]	Ong (319)	No	Alternate Etiology: Diverticulosis

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Study No./ Phase	Subject/Age/ Gender	Adverse Event (MedDRA Preferred Term)	Relationship to Study Drug	Day of Onset ^a	Duration (Days) ^b	D/C	Comment
Febuxostat 80 mg (N=1674)							
C02-021/3	4029/49/Male	Coronary Artery Stenosis ^c	Unlikely	264 [467]	5	No	Alternate Etiology: Underlying coronary artery disease
C02-021/3	4087/ 84/Male	Respiratory Arrest	Not Related	308 [504]	30	Yes	Alternate Etiology: Complications of surgical procedure, worsening of medical condition. Complications of surgical procedure, Expired due to sepsis
		Hiatus Hernia	Not Related	308 [504]	30	Yes	
C02-021/3	4144/62/Male	Pituitary Tumor Benign ^c	Unlikely	208 [403]	40	Yes	Alternate Etiology: Macroadenoma
C02-021/3	4221/59/Male	Small Intestinal Obstruction	Not Related	271 [472]	5	No	Alternate Etiology: Small bowel obstruction
C02-021/3	4263/65/Male	Myocardial Infarction ^c	Not Related	142 [341]	<1	No	Alternate Etiology: Coronary artery disease
C02-021/3	4313/56/Male	Angina Unstable	Unlikely	288 [489]	Ong (323)	No	Alternate Etiology: Underlying coronary artery disease
C02-021/3	4598/49/Male	Idiopathic Thrombocytopenia Purpura ^d	Probable	177 [313]	16	Yes	

Study No./ Phase	Subject/Age/ Gender	Adverse Event (MedDRA Preferred Term)	Relationship to Study Drug	Day of Onset ^a	Duration (Days) ^b	D/C	Comment
Febuxostat 80 mg (N=1674)							
C02-021/3	4641/49/Male	Angina Pectoris	Not Related	134 [327]	2	No	Alternate Etiology: Coronary artery disease
		Renal Failure Acute	Not Related	178 [371]	Ong	No	
C02-021/3	4893/74/Male	Myocardial Infarction	Unlikely	157 [352]	32	No	Alternate Etiology: Coronary artery disease
C02-009/3	4894/61/Male	Abdominal Strangulated Hernia ^a	Not Related	176	5	No	Event occurred on febuxostat 240 mg QD in Study C02-009
C02-021/3		Cholelithiasis ^c	Not Related	58 [253]	2	No	Alternate Etiology: Liver dysfunction
C02-021/3	4907/56/Male	Pulmonary Embolism	Unlikely	174 [369]	2	No	Alternate Etiology: Genetic
C02-021/3	5000/59/Male	Chronic Obstructive Airway Disease	Not Related	185 [388]	4	No	Alternate Etiology: Medical history COPD, Medical history of heart attack, Medical history of CHF
		Exacerbated	Not Related	185 [388]	4	No	
		Myocardial Infarction	Not Related	185 [388]	4	No	
C02-021/3	6022/65/Male	Cholelithiasis ^c	Not Related	165 [359]	2	No	Alternate Etiology: Gall stones

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 Febuxostat (Uloric)

Study No./Phase	Subject/Age/Gender	Adverse Event (MedDRA Preferred Term)	Relationship to Study Drug	Day of Onset ^a	Duration (Days) ^b	D/C	Comment
Febuxostat 120 mg (N=1068)							
C02-010/3 C02-021/3	2198/52/Female	Cellulitis ^a Gastroesophageal Reflux Disease ^a	Not Related Not Related	15 261 [572]	2 4	No No	Alternate Etiology: Probable GERD
C02-021/3	2221/44/Male	Intestinal Obstruction ^a	Unlikely	262 [630]	2	No	Alternate Etiology: S/P Herniorrhaphy and use of Percocet
C02-010/3 C02-010/3 C02-021/3	2426/58/Male	Rectal Hemorrhage ^a Pancreatitis Chronic ^d Obesity ^e	Unlikely Unlikely Not Related	221 224 182 [560]	4 9 2	No No No	Alternate Etiology: Pre-existing Condition
C02-010/3 C02-021/3 C02-021/3	2610/62/Male	Atrial Fibrillation ^a Localised Osteoarthritis ^d Localised Osteoarthritis	Not Related Not Related Not Related	262 [317] 63 [420] 206 [363]	4 <1 5	No No No	Alternate Etiology: CAD Alternate Etiology: DHD Alternate Etiology: DJD
C02-021/3	2789/50/Male	Chest Pain	Not Related	125 [494]	<1	No	Alternate Etiology: Probable Muscular Pain
Febuxostat 120 mg (N=1068)							
C02-021/3	4057/60/Male	Vertigo ^c Vertigo ^e	Not Related Not Related	109 [304] 169 [364]	4 5	No No	Events previously reported as Ischemic Stroke and Cardiac Failure Congestive. Age at time of study entry for Study C02-009. AE onset day is from start of C02-021. Alternate Etiology: Middle/lower ear disease and/or old lacunar infarction
C02-021/3	4165/54/Female	Ovarian Cyst ^a	Unlikely	163 [361]	2	Yes	Alternate Etiology: Hormonal stimulation
C02-021/3	4175/65/Male	Cardiac Failure Congestive ^d Cardiac Failure Congestive	Unlikely Unlikely	39 [236] 60 [257]	33 12	No Yes	Age at time of study entry for Study C02-009. AE onset day is from start of C02-021. Alternate Etiology: Congestive heart failure. Pre-existing congestive heart failure
C02-021/3	4329/50/Male	Myocardial Infarction ^a	Not Related	204 [404]	3	No	Alternate Etiology: Cardiac history
C02-021/3	4350/58/Male	Osteoarthritis	Not Related	267 [463]	4	No	Alternate Etiology: Osteoarthritis

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Study No./Phase	Subject/Age/Gender	Adverse Event (MedDRA Preferred Term)	Relationship to Study Drug	Day of Onset ^a	Duration (Days) ^b	D/C	Comment
Febuxostat 120 mg (N=1068)							
C02-021/3	4744/59/Male	Atrial Fibrillation Atrial Fibrillation	Not Related Not Related	177 [377] 226 [426]	8 3	No No	Alternate Etiology: Cardiac arrhythmia, Cardiac arrhythmia
C02-021/3	4753/52/Male	Cardiac Failure Congestive	Unlikely	250 [442]	10	No	Alternate Etiology: uncontrolled hypertension
C02-021/3	4963/80/Female	Myocardial Infarction ^c	Not Related	84 [280]	Unk	No	Event occurred on Febuxostat 80 mg QD
		Renal Artery Stenosis	Not Related	211 [407]	2	No	Alternate Etiology: Coronary artery disease Alternate Etiology: Peripheral vascular disease
Allopurinol 300/100 mg OD (N=643)							
C02-021/3	2543/58/Male	Diverticulitis ^d	Unlikely	148 [513]	5	No	Alternate Etiology: Natural causes - diverticulitis
C02-021/3	2808/61/Male	Abdominal Strangulated Hernia	Not Related	284 [646]	3	No	Alternate Etiology: mechanical obstruction
C02-021/3	4484/56/Male	Appendicitis ^e	Not Related	192 [391]	2	No	
C02-021/3	4674/60/Male	Coronary Artery Disease ^f	Unlikely	85 [288]	27	No	Alternate Etiology: Coronary Artery Disease
C02-021/3	4950/39/Male	Deep Vein Thrombosis Pulmonary Embolism	Unlikely Unlikely	171 [367] 171 [367]	7 7	No No	Alternate Etiology: Deep Vein Thrombosis, Deep Vein Thrombosis of right arm

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Table 10 (Sponsor's Table 3.4.d, SU) Other Serious Adverse Events (Initial Reports) Occurring in Studies TMX-01-005 and C02-021 Between 29 October 2004 and 31 December 2004

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Study No./Phase	Subject/Age/Gender	Adverse Event (MedDRA Preferred Term)	Relationship to Study Drug	Day of Onset ^a	Duration (Days)	D/C	Comment
Febuxostat 80 mg QD (N=1225)							
C02-021/3	2062/74/Male	Hemiparesis Electroencephalogram Abnormal	Possible Possible	433 [433] 434 [434]	<1 Ongoing	No	Expedited Report
C02-021/3	2482/64/Male	Cholelithiasis	Unlikely	382 [746]	6	No	
C02-021/3	4756/52/Male	Cerebrovascular Accident	Not Related	271 [467]	3	No	
C02-021/3	2055/72/Female	Cerebrovascular Accident	Unlikely	465 [833]	Ongoing	Yes	
C02-021/3	2214/40/Male	Nephrolithiasis	Unlikely	433 [722]	Ongoing	No	
C02-021/3	4753/54/Male	Diabetes Mellitus Non-Insulin Dependent	Not Related	304 [304]	Ongoing	Unk	Switched from allopurinol to febuxostat on Day 35; SAE of congestive heart failure on Day 251 in Study C02-021
Febuxostat 120 mg QD (N=932)							
TMX-01-005/2	1150/44/Male	Intervertebral Disc Degeneration	Not Related	1233 [1261]	2	No	
C02-021/3	4775/66/Male	Coronary Artery Disease	Not Related	281 [377]	2	No	Prior SAE of Transient Ischemic Attack in Study C02-009
C02-021/3	4916/68/Male	Cerebrovascular Accident	Unlikely	236 [464]	Ongoing	No	
C02-021/3	4186/87/Female	Atrial Fibrillation ^a Exacerbation of Chronic Obstructive Pulmonary Disease ^b	Not Related Not Related	406 406	Unknown Unknown	Yes	Alternative Etiology: History of COPD and "on coumadin". Subject expired due to retroperitoneal hemorrhage ^c

D/C = discontinuation; AE = adverse event; SAE = serious adverse event; Unk = unknown
 a Cumulative febuxostat days are shown in brackets
 b Event occurred after 31 December 2004
 Cross-reference: TAP Pharmacovigilance Database

No additional SAEs were reported in the Japan Clinical program for 4-month safety update.

Reviewer's comments:

- Review of patients' narratives of deaths, SAEs, and discontinuations due to AEs (included trials TMX-00-004, TMX-01-005, C02-009, C02-010, and C02-021, is summarized in the following table:

Table 11. Summary table of SAEs, including deaths

	Placebo (N=172)	Allopurinol 300/100 mg (N=692)	Febuxostat Total (N=1707)
Coronary Artery Disorders (coronary artery atherosclerosis, CAD, CA occlusion)	1	5	6
CHF	0	1	8
Ischemic CAD (acute coronary syndrome, acute MI, angina, MI)	0	2, incl. 1 MI+ 1 angina	17, including 12 MIs+ 4 angina+ 1 acs
Atrial fibrillation, supraventricular tachycardias (SVT)	0	0	8 (7 A-fib+ 1 SVT)
Cardiac arrest	0	0	2
CVA, TIA	0	0	7+2TIA
PE	0	1	2

DVT	0	0	1
Acute Hepatitis	0	0	1
Colon cancer metast.	0	0	2
Benign pituitary tumor	0	1	0
Parathyroid malignant tumor	0	0	1
Hodgkin's	0	1	0
Tongue neoplasm malign.	0	0	1
Prostate cancer	0	0	2
Benign lung neoplasm	0	0	1
Basal cell CA	0	0	1
Testicular germ cell CA	0	1	0
Guillain-Barre syndrome	0	0	1
ITP	0	0	1
Renal failure/insufficiency/impairment	0	0	3
Total thrombotic events (MI, stroke)		1	19

- *There is a concern that overall febuxostat causes more SAEs than a comparator allopurinol*
- ***Cardiovascular AEs, and thrombotic events in particular, in febuxostat treatment groups present a significant concern. There is a significant difference in the number of cardio-vascular AEs due to febuxostat (all doses) compared to allopurinol or placebo. For combined thromboembolic events such as fatal and non-fatal MIs and strokes, the difference is 19/1707 vs. 1/692.***
- *There were 3 cases of renal impairment in patient on febuxostat compared to zero in allopurinol groups*
- *In this reviewer's opinion, in most cases of SAEs, other than neoplasms, a causal association with the treatment drug cannot be excluded*
- *There were some differences noted from review of patients' narratives that is some cases cardio-vascular events such as MI were not considered an SAE and were not coded as cardio-vascular.*
- *There is no obvious dose-relationship but the numbers are relatively small and might not allow a determination of a dose-response*
- *Of note, placebo treatment did not continue beyond 6 months, while 202 subjects in active treatment arms (both febuxostat and allopurinol) continued ≥18 months*
- *4-months safety update added 1 case of prostate CA, one case of B-cell lymphoma, four cases of an MI, one of CAD /CABG, one-of unstable angina, one-of ARF, one -of CVA (brain steam infarction), one-of pulmonary embolism/DVT, two of A-fib, one- of CHF; for allopurinol: one of CAD, one of DVT/PE*
- *From October 29, 2004 and December 31, 2004, additional 3 cases of CVA, one case of possible TIA and one case of a coronary artery disease with angioplasty were observed in febuxostat groups*
- *Review of patients' narratives revealed three cases of SAE where INR values were 4.3-10 in patients on concomitant febuxostat and coumadin (4518, 4551, 2024). This reviewer concludes that co-administration of febuxostat and warfarin/coumadin was not adequately studied*

b(4)

- *Interestingly, the nature of SAEs in Japan clinical program seems to be different and less of concern compared to SAEs in US program. This could be related to a lower dose of febuxostat used in Japan program*

7.1.3 Dropouts and Other Significant Adverse Events

Among subjects who participated in the United States Phase 2/3 febuxostat clinical program, 162 (127 of 1707 receiving febuxostat, 27 of 629 receiving allopurinol 300/100 mg QD, and 8 of 172 receiving placebo) prematurely discontinued from study drug at least in part due to 1 or more adverse events occurring after the first dose of study drug and within 30 days of a subject's final dose.

7.1.3.1 Overall profile of dropouts .

Table 12 (Sponsor's Table 2.2a) Reasons for Premature Discontinuation (Phase 2/3 Studies)

	Treatment Group n (%)						
	Placebo (N=172)	Febuxostat					Allopurinol 300/100 mg QD (N=629)
		All Doses (N=1707)	40 mg (N=46)	80 mg QD (N=1180)	120 mg QD (N=876)	240 mg QD (N=134)	
Completed Study ^a	137 (80%)	1207 (71%)	43 (93%)	937 (79%)	670 (76%)	86 (64%)	495 (79%)
Prematurely Discontinued	35 (20%)	500 (29%)	3 (7%)	243 (21%)	206 (24%)	48 (36%)	134 (21%)
Primary Reason:							
Adverse event	6 (3%)	114 (7%)	2 (4%)	54 (5%)	47 (5%)	11 (8%)	26 (4%)
Lost to follow-up	10 (6%)	102 (6%)	0	53 (4%)	40 (5%)	9 (7%)	40 (6%)
Personal reason(s)	9 (5%)	93 (5%)	0	49 (4%)	35 (4%)	9 (7%)	22 (3%)
Other ^b	3 (2%)	76 (4%)	1 (2%)	38 (3%)	31 (4%)	6 (4%)	26 (4%)
Gout flare	1 (<1%)	76 (4%)	0	28 (2%)	40 (5%)	8 (6%)	10 (2%)
Protocol violation	3 (2%)	24 (1%)	0	15 (1%)	6 (<1%)	3 (2%)	7 (1%)
Therapeutic failure	3 (2%)	15 (<1%)	0	6 (<1%)	7 (<1%)	2 (1%)	3 (<1%)

Phase 2/3 studies included: TMX-00-004, TMX-01-005, C02-009, C02-010, and C02-021.

a A total of 1069 subjects (67 of 116 in Study TMX-01-005 and 1002 of 1074 in Study C02-021) are ongoing.

b "Other" reasons included: unstable lab results, sponsor request, vacation, withdrew consent, noncompliance, investigator request, serum urate level not controlled/lack of efficacy, doctor's decision due to concern with subject not being on allopurinol causing kidney stones, move out of state, need for prohibited medication, elevated liver function, sponsor request, 24-hour Cl_{cr} below entry criteria, kidney donation, concern over persistently elevated blood pressure, administrative reasons, several gout flares, subject unblinded study drug, inability to discontinue exclusionary medication, difficulty assessing disease under study due to concurrent diagnosis (osteoarthritis), sponsor terminated study at site, abnormal lab values, inability to speak or read English and provide consent, and site closure/transfer site too far.

Cross-reference: Statistical Table 2.2.2 and Appendix 16 2-1.1 from Studies TMX-00-004, TMX-01-005, C02-009, C02-010, and C02-021

Reviewer's comments:

- *Overall, there is no difference between treatment groups in the proportion of patients who prematurely discontinued from the trial*
- *Among reasons for premature discontinuation in phase 2/3 trials, the following looks worse for febuxostat compared to allopurinol:*

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- **Overall discontinuation due to adverse events is worse in febuxostat group (7%, driven by higher rate of discontinuations in 240 mg dose group) followed by allopurinol (4%) and placebo (3%) groups.**
- **Gout flare: 4.4% in febuxostat, 1.6% in allopurinol and 0% in placebo group discontinued due to gout flare;**
- **Therapeutic failure: discontinued 0.8% of patients in febuxostat group, 0.4% in allopurinol group and 1.7% in placebo group.**
- **Substantial number of patients were lost to follow up, discontinued for personal reasons or other reasons in all treatment groups, and those numbers are significantly higher than what we usually see in other drugs' development programs**

7.1.2.2 Adverse events associated with dropouts

Table 13 (Sponsor's Table 3.5a, ISS)
Adverse Events Leading to Premature Discontinuation Occurring in ≥1% and at Least 2 Subjects in Any Treatment Group (Phase 2/3 Studies)

MedDRA High Level Term MedDRA Preferred Term	Treatment Group n (%)						
	Placebo (N=172)	Febuxostat					Allopurinol (N=629)
		All Doses (N=170)	40 mg QD (N=46)	80 mg QD (N=118)	120 mg QD (N=87)	240 mg QD (N=134)	
Premature Discontinuations Due to Treatment-Emergent Adverse Events							
Total Subjects with at Least 1 Adverse Event	8 (5%)	127 (7%)	3 (7%)	59 (5%)	52 (6%)	13 (10%)	27 (4%)
Diarrhoea (Excl Infective)	1 (<1%)	8 (<1%)	0	2 (<1%)	2 (<1%)	4 (3%)	2 (<1%)
Diarrhoea	0	5 (<1%)	0	1 (<1%)	0	4 (3%)	2 (<1%)
Nausea & Vomiting Symptoms Nausea, Vomiting	0	25 (1%)	1 (2%)	14 (1%)	10 (1%)	0	5 (<1%)
Liver Function Analyses Alanine Aminotransferase Increased, Aspartate Aminotransferase Increased, Blood Bilirubin Increased, Hepatic Enzyme Increased, Liver Function Test Abnormal	0	7 (<1%)	1 (2%)	3 (<1%)	3 (<1%)	0	1 (<1%)
Renal Function Analyses Blood Creatinine Increased, Blood Urea Increased, Creatinine Renal Clearance Decreased	0	3 (<1%)	0	0	0	3 (2%)	1 (<1%)
Neurological Signs & Symptoms NEC Dizziness	0	0	0	0	0	0	0
Premature Discontinuations Due to Treatment-Related Adverse Events							
Total Subjects with at Least 1 Adverse Event	6 (3%)	77 (5%)	3 (7%)	37 (3%)	29 (3%)	8 (6%)	16 (3%)
Diarrhoea (Excl Infective)	1 (<1%)	5 (<1%)	0	1 (<1%)	1 (<1%)	3 (2%)	2 (<1%)
Diarrhoea	0	3 (<1%)	0	0	0	3 (2%)	1 (<1%)
Nausea & Vomiting Symptoms Nausea, Vomiting	0	21 (1%)	1 (2%)	11 (<1%)	9 (1%)	0	4 (<1%)
Liver Function Analyses Alanine Aminotransferase Increased, Aspartate Aminotransferase Increased, Blood Bilirubin Increased, Hepatic Enzyme Increased, Liver Function Test Abnormal	0	0	0	0	0	0	0

NEC = not elsewhere classified
Phase 2/3 studies included: TMX-09-004, TMX-01-005, C02-009, C02-010, and C0-021.
Cross-reference: Statistical Tables 3.10.2 and 3.11.2

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ON ORIGINAL

Reviewer's comment:

- *In the Phase 2/3 studies, the incidence of premature discontinuations due to treatment-emergent adverse events was the highest in the febuxostat 120 mg QD (10%), followed by other doses of febuxostat and, placebo (5%); allopurinol 300/100 mg QD had the lowest rate of 4%*
- *The most common AE that led to discontinuation from the study drug was liver function abnormalities in febuxostat treatment groups, and those AEs were numerically higher than in allopurinol group. This might represent a signal for potential liver toxicity*
- *Renal function abnormalities were also more common in febuxostat group compared to allopurinol group*
- *There seems to be no difference in the incidence of premature discontinuations due to treatment-emergent adverse events between febuxostat 80 mg and 120 mg groups*

Table 14 (Sponsor's Table 3.5b)
Adverse Events Leading to Premature Discontinuation Occurring in $\geq 1\%$ and at Least 2
Subjects in Any Treatment Group (Phase 2/3 Studies)
4-Month Safety Update

APPEARS THIS WAY
ON ORIGINAL

MedDRA High Level Term MedDRA Preferred Term	Treatment Group n (%)						
	Placebo	Febuxostat					Allopurinol
	(N=172)	All Doses (N=1720)	40 mg QD (N=48)	80 mg QD (N=1225)	120 mg QD (N=932)	240 mg QD (N=134)	300/100 mg QD (N=643)
Premature Discontinuations Due to Treatment-Emergent Adverse Events							
Total Subjects with at Least 1 Adverse Event	8 (5%)	142 (8%)	3 (6%)	70 (6%)	56 (6%)	13 (10%)	28 (4%)
Diarrhoea (Excl Infective)	1 (<1%)	10 (<1%)	0	3 (<1%)	3 (<1%)	4 (3%)	2 (<1%)
Diarrhoea							
Nausea & Vomiting Symptoms	0	5 (<1%)	0	1 (<1%)	0	4 (3%)	2 (<1%)
Nausea, Vomiting							
Liver Function Analyses	0	27 (2%)	1 (2%)	15 (1%)	11 (1%)	0	6 (<1%)
ALT Increased, AST Increased, Blood Bilirubin Increased, Hepatic Enzyme Increased, LFT Abnormal							
Renal Function Analyses	0	8 (<1%)	1 (2%)	3 (<1%)	4 (<1%)	0	1 (<1%)
Blood Creatinine Increased, Blood Urea Increased, Creatinine Renal Clearance Decreased							
Neurological Signs & Symptoms NEC	0	3 (<1%)	0	0	0	3 (2%)	1 (<1%)
Dizziness							
Premature Discontinuations Due to Treatment-Related Adverse Events							
Total Subjects with at Least 1 Adverse Event	6 (3%)	81 (5%)	3 (6%)	37 (3%)	33 (4%)	8 (6%)	17 (3%)
Diarrhoea (Excl Infective)	1 (<1%)	7 (<1%)	0	2 (<1%)	2 (<1%)	3 (2%)	2 (<1%)
Diarrhoea							
Nausea & Vomiting Symptoms	0	3 (<1%)	0	0	0	3 (2%)	1 (<1%)
Nausea, Vomiting							
Liver Function Analyses	0	22 (1%)	1 (2%)	11 (<1%)	10 (1%)	0	5 (<1%)
ALT Increased, AST Increased, Blood Bilirubin Increased, Hepatic Enzyme Increased, LFT Abnormal							
Neurological Signs & Symptoms NEC	0	2 (<1%)	0	0	0	2 (1%)	0
Dizziness							

NEC = not elsewhere classified

Studies included: TMX-00-004, TMX-01-005, C02-009, C02-010, and C0-021

Subjects who received study drug from more than 1 dose group are counted in each of the dose groups.

Adverse events summarized were reported after the first dose of study drug and within 30 days of the last dose of study drug. Subjects with 1 or more adverse events within a level of the MedDRA term are counted only in that level.

Cross-reference: Updated Statistical Tables 3.10.2.1 and 3.11.2.1

Reviewer's comment:

- *There was an increase in the incidence of premature discontinuations due to treatment-emergent adverse events from 5% to 6% for the febuxostat 80 mg QD group when compared to the ISS, while the incidences for the febuxostat 120 mg QD and allopurinol 300/100 mg QD treatment groups remained unchanged*

- *The pattern of all adverse events causing withdrawal from study drug did not change when compared to the ISS, and was hepatic, rash, and gastrointestinal in nature*
- *Febuxostat groups have higher rates of premature discontinuations due to liver function and renal function abnormalities compared to allopurinol groups*
- *There seems to be no difference in the incidence of premature discontinuations due to treatment-emergent adverse events between febuxostat 80 mg and 120 mg groups*
- *The incidence of treatment-emergent events of diarrhea and nausea leading to premature discontinuations is noticeably higher in the febuxostat 240 mg QD group. The possible explanation to this could be an associated concomitant use of colchicine in these subjects (see below)*

The United States Phase 2/3 clinical febuxostat program was conducted with NSAIDs or colchicine prophylaxis during the first 2-4 weeks (Phase 2) or 8 weeks (Phase 3) of the studies. Colchicine has known side effects, which include diarrhoea, nausea, and vomiting. Furthermore, subjects in the febuxostat 240 mg QD treatment group may have had increased use of these agents due to gout flares. Thus, the association between colchicine and the incidence of premature discontinuations was analyzed.

When only those adverse events leading to premature discontinuation were counted while a subject was not taking colchicine, the overall incidence of premature discontinuations due to adverse events in the Phase 3 controlled studies was 4%, 6%, and 3% in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups, respectively, and 3% and 3% in the febuxostat 240 mg QD and placebo treatment groups, respectively (Table 15).

Table 15 (Sponsor's Table 3.5c, ISS) Adverse Events Leading to Premature Discontinuation Occurring in $\geq 1\%$ and at Least 2 Subjects in Any Treatment Group while Subjects Were Not Taking Colchicine (Phase 3 Controlled Studies)

MedDRA High Level Term MedDRA Preferred Term	Treatment Group n (%)				
	Placebo (N=134)	Febuxostat 80 mg QD (N=523)	Febuxostat 120 mg QD (N=518)	Febuxostat 240 mg QD (N=132)	Allopurinol 300/100 mg QD (N=521)
Premature Discontinuations Due to Treatment-Emergent Adverse Events					
Total Subjects with at Least 1 Adverse Event	4 (3%)	23 (4%)	29 (6%)	4 (3%)	18 (3%)
Liver Function Analyses					
Alanine Aminotransferase Increased, Aspartate Aminotransferase Increased, Blood Bilirubin Increased, Hepatic Enzyme Increased, Liver Function Test Abnormal	0	6 (1%)	7 (1%)	0	4 (<1%)

Phase 3 studies included: C02-009 and C02-010 combined data.
 Cross-reference: Statistical Table 6.13.5

A total of 19 subjects prematurely discontinued study drug due to an adverse event in the Japan clinical program. The most frequently reported adverse event leading to premature discontinuation of study drug were events associated with rash (including the preferred terms rash, rash generalized, and urticaria) and hepatic abnormalities (including the preferred terms aspartate aminotransferase increased, alanine aminotransferase increased, blood lactate dehydrogenase increased, and gamma-glutamyltransferase increased).

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 ON ORIGINAL

7.1.2.3 Other significant adverse events

Laboratory values that were considered potentially concerning are discussed in **Section 7.1.5**. Electrocardiograms that were considered to have clinically significant changes from baseline are discussed in **Section 7.1.7**.

Since this reviewers rose a concern about increased risk of cardio-vascular (CV) adverse events associated with febuxostat treatment, below is an assessment of the Sponsor's analysis of CV adverse events. Since not all CV AEs were severe adverse events (SAE), they are reviewed here under "other significant AEs".

The Sponsor's estimated incidence of treatment-emergent cardiovascular adverse events in 4-month safety update was 8% (5% in ISS), 6% (5%), and 6% (6%) in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups, respectively (**Table 16**). This reflects an increase in the incidence in the febuxostat 80 mg QD and 120 mg QD group which the Sponsor suggests is likely due to the relatively greater increase in exposure in these 2 groups when compared to the allopurinol 300/100 mg QD group.

Treatment-emergent cardiovascular adverse events for the 4-month safety update are summarized in **Table 16**.

Table 16 (Sponsor's Table 3.6.a, SU)

Incidence of Treatment-Emergent Cardiovascular and Hypertension Adverse Events Occurring in 1% of Subjects in Phase 2/3 Studies - 4-Month Safety Update

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ON ORIGINAL

MedDRA High Level Term MedDRA Preferred Terms	Treatment Group n (%)						
	Placebo (N=172)	Febuxostat					Allopurinol 300/100 mg QD (N=643)
		All Doses (N=1720)	40 mg QD (N=48)	80 mg QD (N=1225)	120 mg QD (N=932)	240 mg QD (N=134)	
Cardiovascular Adverse Events							
Total Subjects with at Least 1 Adverse Event	4 (2%)	155 (9%)	3 (6%)	92 (8%)	37 (6%)	9 (7%)	39 (6%)
Ischaemic Coronary Artery Disorders NEC	0	27 (2%)	0	14 (1%)	12 (1%)	1 (<1%)	3 (<1%)
Acute Coronary Syndrome, Acute Myocardial Infarction, Angina Pectoris, Angina Unstable, Myocardial Infarction, Silent Myocardial Infarction	0	16 (<1%)	0	8 (<1%)	6 (<1%)	2 (1%)	3 (<1%)
Supraventricular Arrhythmias	0	8 (<1%)	0	4 (<1%)	2 (<1%)	2 (1%)	1 (<1%)
Atrial Fibrillation, Atrial Flutter, Atrial Tachycardia, Sinus Bradycardia, Sinus Tachycardia, Supraventricular Extrasystoles, Supraventricular Tachycardia	0	8 (<1%)	0	4 (<1%)	2 (<1%)	2 (1%)	1 (<1%)
General Signs and Symptoms NEC	1 (<1%)	28 (2%)	0	17 (1%)	9 (<1%)	2 (1%)	5 (<1%)
Chest Discomfort Pain and Discomfort NEC Chest Pain	1 (<1%)	28 (2%)	0	17 (1%)	9 (<1%)	2 (1%)	5 (<1%)

Studies included: TMAX-00-004, TMAX-01-025, C02-009, C02-010, and C0-021
Subjects who received study drug from more than 1 dose group are counted in each of the dose groups. Adverse events summarized were reported after the first dose of study drug and within 30 days of the last dose of study drug. Subjects with 1 or more adverse events within a level of the MedDRA term are counted only in that level.
Cross-Reference: Updated Statistical Table 3.12.2.1.1, 3.12.2.2

Reviewer's comments:

- The AEs of interest are summarized under Ischemic Coronary Artery Disorders subgroup. From this reviewer point of view, the difference in the incidence of those events between febuxostat and allopurinol group is significant: 27/1720, or 1.6% vs. 3/643, or 0.4%.

Because of the differences in exposure between febuxostat and allopurinol-treated subjects, the Sponsor performed an additional analysis of cardiovascular adverse events by patient-years of exposure for the Phase 2/3 studies (Table 17). In this table, the percentages are the adverse event rates per 100 patient-years of exposure.

The Sponsor's conclusion was that the overall incidence by patient-years of exposure was similar across the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups (12%, 12%, and 14%, respectively). In the placebo, febuxostat 40 mg QD and the febuxostat 240 mg QD group, the overall incidence was 8%, 17%, and 17%, respectively.

**Table 17 (Sponsor's Table 3.6.b, SU)
Incidence of Treatment-Emergent Cardiovascular Adverse Events by Patient-Years of Exposure Occurring in 1% of Subjects in Phase 2/3 Studies - 4-Month Safety Update**

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MedDRA High Level Term MedDRA Preferred Terms	Treatment Group n (%)						
	Placebo	Febuxostat				Allopurinol	
		All Doses	40 mg QD	80 mg QD	120 mg QD	240 mg QD	300/100 mg QD
Patient-years of Exposure	63	1712	29	1012	617	51	407
Total Number of Adverse Events	5 (8%)	211 (12%)	5 (17%)	121 (12%)	73 (12%)	9 (17%)	55 (14%)
Cardiac Conduction Disorders Atrioventricular Block First Degree, Atrioventricular Block Second Degree, Bundle Branch Block Left, Bundle Branch Block Right	0	4 (<1%)	1 (3%)	3 (<1%)	0	0	2 (<1%)
Cardiac Disorders NEC Cardiovascular Disorder, Diastolic Function	0	1 (<1%)	1 (3%)	0	0	0	2 (<1%)
Cardiac Signs and Symptoms NEC Palpitations	0	6 (<1%)	0	1 (<1%)	4 (<1%)	1 (2%)	6 (1%)
Coronary Artery Disorders NEC Coronary Artery Atherosclerosis, Coronary Artery Disease, Coronary Artery Occlusion, Coronary Artery Stenosis	2 (3%)	11 (<1%)	0	9 (<1%)	2 (<1%)	0	6 (1%)
Ischemic Coronary Artery Disorders NEC Acute Coronary Syndrome, Acute Myocardial Infarction, Angina Pectoris, Angina Unstable, Myocardial Infarction, Silent Myocardial Infarction	0	28 (2%)	0	18 (1%)	12 (2%)	1 (2%)	3 (<1%)
Myocardial Disorders Cardiomegaly, Dilatation Ventricular, Ventricular Rupture, Ventricular Dysfunction, Ventricular Hypertrophy, Ventricular Hypokinnesia	0	2 (<1%)	0	2 (<1%)	0	0	3 (1%)
Rate and Rhythm Disorders Arrhythmia, Bradycardia, Extrasystoles, Tachycardia	1 (2%)	12 (<1%)	0	9 (<1%)	3 (<1%)	0	3 (<1%)

Studies included: TMX-00-004, TMX-01-005, C02-009, C02-010, and C0-021
Subjects who received study drug from more than 1 dose group are counted in each of the dose groups. Adverse events summarized were reported after the first dose of study drug and within 30 days of the last dose of study drug.
The percentages are the adverse event rates per 100 patient-years of exposure.
Cross-Reference: Updated Statistical Table 3.12.2.1.2.

APPEARS THIS WAY
ON ORIGINAL

Reviewer's comments:

- The AEs of interest are summarized under Ischemic Coronary Artery Disorders subgroup.
- Of note, the number of AEs in this subgroup is 28 vs. 27 in Table 16 (no explanation was found)
- From this reviewer point of view, the difference in the incidence of those events between febuxostat and allopurinol group is significant: 28/1712 pt/yrs, or 1.6% vs. 3/407 pt/yrs, or 0.7%.

Furthermore, the Sponsor performed an additional analysis was by identifying those MedDRA preferred terms that indicate a thrombo-embolic adverse event (Table 18). The overall incidence of treatment-emergent thrombo-embolic adverse events by patient-years of exposure in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD groups was 3%, 3%, and 2%, respectively, and the overall incidence in the placebo, febuxostat 40 mg QD and febuxostat 240 mg QD groups was 3%, 3%, and 2%, respectively. The Sponsor's conclusion was that the incidence of specific treatment-emergent thrombo-embolic adverse events was low and similar across groups.

Table 18 (Sponsor's Table 3.6.c, SU)

Incidence of Treatment-Emergent Thrombo-Embolic Adverse Events by Patient-Years of Exposure Occurring in 1% of Subjects in Phase 2/3 Studies - 4-Month Safety Update

MedDRA High Level Term MedDRA Preferred Terms	Treatment Group n (%)						
	Placebo	Febuxostat					Allopurinol
		All Doses	40 mg QD	80 mg QD	120 mg QD	240 mg QD	
Patient-years of Exposure	63	1712	29	1012	617	54	407
Total Number of Adverse Event	2 (3%)	49 (3%)	1 (3%)	29 (3%)	18 (3%)	1 (2%)	10 (2%)
Coronary Artery Disorders NEC Coronary Artery Atherosclerosis, Coronary Artery Disease, Coronary Artery Occlusion, Coronary Artery Stenosis	2 (3%)	11 (<1%)	0	9 (<1%)	2 (<1%)	0	6 (1%)
Ischaemic Coronary Artery Disorders NEC Acute Coronary Syndrome, Acute Myocardial Infarction, Angina Pectoris, Angina Unstable, Myocardial Infarction, Silent Myocardial Infarction	0	28 (2%)	0	15 (1%)	12 (2%)	1 (2%)	3 (<1%)

Studies included: TMX-00-004, TMX-01-005, C02-009, C02-010, and C0-021

Subjects who received study drug from more than 1 dose group are counted in each of the dose groups. Adverse events summarized were reported after the first dose of study drug and within 30 days of the last dose of study drug.

The percentages are the adverse event rates per 100 patient-years of exposure.

Cross-Reference: Updated Statistical Table 3.12.2.1.3

APPEARS THIS WAY ON ORIGINAL

Reviewer's comments:

- The AEs of interest are summarized under Ischemic Coronary Artery Disorders subgroup.
- Of note, events such as strokes, PE, DVT that represent thrombo-embolic events as well, are not included into analysis
- Events such as acute coronary syndrome, angina, angina unstable are not necessarily thrombo-embolic in nature
- From this reviewer point of view, the difference in the incidence of those events between febuxostat and allopurinol group is significant: 28/1712 pt/yrs, or 1.6% vs. 3/407 pt/yrs, or 0.7%.

7.1.3 Common Adverse Events

7.1.3.1 Eliciting adverse events data in the development program

An adverse event was defined as any unfavorable, unintended or untoward sign, symptom or disease temporally associated with use of a medicinal product, whether or not considered related to the medicinal product. Throughout the studies, the investigator closely monitored each subject for evidence of drug intolerance and for the development of clinical or laboratory evidence of adverse events. All adverse events (expected and unexpected), whether observed by the investigator or by the subject, and whether or not thought to be drug-related, were reported in detail on the appropriate case report form (CRF) and followed to a satisfactory resolution.

Gout flares were considered to be exacerbation of the underlying disease were not captured as adverse events as these were considered measures of efficacy and discussed in the Integrated

Summary of Efficacy. However, if a gout flare met 1 of the conditions listed below for a serious adverse event, it was captured as a serious adverse event in the TAP Pharmacovigilance database only. Therefore, gout flare serious adverse events are not included in the statistical tables.

7.1.3.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were coded using the MedDRA coding dictionary. Individual studies were coded using versions of Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) or MedDRA current at the time of each CSR, but all adverse events from all studies have been recoded to MedDRA Version 7.0 for summarization in the ISS. Thus, some differences in coding may be noted when comparing the ISS to individual CSRs.

The Medical Dictionary for Regulatory Activities (MedDRA) preferred terms reported in the Phase 3 controlled studies were reviewed and specific terms were identified and included in the organ system of interest.

7.1.3.3 Incidence of common adverse events

In the **Phase 2/3 studies**, the overall incidence of treatment-emergent adverse events in ISS was 60%, 57%, and 70% in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups, respectively, and 73%, 63%, and 67% in the febuxostat 240 mg QD, febuxostat 40 mg QD, and placebo treatment groups, respectively. In the febuxostat total group, the overall incidence of treatment-emergent adverse events was 68%.

Of note, the incidence of the HLT edema not elsewhere classified (NEC) was 3%, 2%, and 2% in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups and 4%, 0%, and <1% in the febuxostat 240 mg QD, febuxostat 40 mg QD, and placebo treatment groups, respectively.

The incidence of specific treatment-emergent preferred terms such as diarrhea, was 7%, 7%, and 5% in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups, respectively, and 13%, 7%, and 8% in the febuxostat 240 mg QD, febuxostat 40 mg QD, and placebo treatment groups, respectively.

The overall incidence of treatment-emergent adverse events in the **Phase 3** controlled studies was 74%, 72%, and 80% in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups, respectively, and 73% and 72% in the febuxostat 240 mg QD and placebo treatment groups, respectively.

Table 19 (Sponsor's Table 3.2a, ISS) Treatment-Emergent Adverse Events Occurring in $\geq 5\%$ of Subjects in Any Treatment Group (Phase 2/3 Studies)

MedDRA High Level Term MedDRA Preferred Terms	Treatment Group n (%)						
	Placebo (N=172)	Febuxostat					Allopurinol (N=629)
		All Doses (N=1707)	40 mg QD (N=46)	80 mg QD (N=1180)	120 mg QD (N=876)	240 mg QD (N=134)	
Total Subjects with at Least 1 Adverse Event	116 (67%)	1156 (68%)	29 (63%)	707 (60%)	500 (57%)	98 (73%)	441 (70%)
Upper Respiratory Tract Infections Acute Sinusitis, Acute Tonsillitis, Laryngitis, Nasopharyngitis, Pharyngitis, Rhinitis, Sinusitis, Tonsillitis, Upper Respiratory Tract Infection	25 (15%)	376 (22%)	6 (13%)	221 (19%)	141 (16%)	27 (20%)	136 (22%)
Diarrhoea (Excl Infective)	14 (8%)	156 (9%)	3 (7%)	80 (7%)	60 (7%)	18 (13%)	34 (5%)
Musculoskeletal & Connective Tissue Signs & Symptoms NEC Back Pain, Buttock Pain, Chest Wall Pain, Dupuytren's Contracture, Flank Pain, Limb Discomfort, Muscle Spasms, Musculoskeletal Chest Pain, Musculoskeletal Discomfort, Musculoskeletal Pain, Musculoskeletal Stiffness, Neck Pain, Nodule on Extremity, Pain in Extremity	17 (10%)	194 (11%)	6 (13%)	105 (9%)	75 (9%)	14 (10%)	68 (11%)

NEC = not elsewhere classified
Phase 2/3 studies included: TMX-00-004, TMX-01-005, C02-009, C02-010, and C02-021.
Cross-reference: Statistical Tables 3.1.2 and 3.3.2

MedDRA High Level Term MedDRA Preferred Terms	Treatment Group n (%)						
	Placebo (N=172)	Febuxostat					Allopurinol (N=629)
		All Doses (N=1707)	40 mg QD (N=46)	80 mg QD (N=1180)	120 mg QD (N=876)	240 mg QD (N=134)	
Joint Related Signs & Symptoms Arthralgia, Joint Crepitation, Joint Effusion, Joint Range of Motion Decreased, Joint Stiffness, Joint Swelling, Temporomandibular Joint Syndrome	9 (5%)	180 (11%)	5 (11%)	104 (9%)	66 (8%)	7 (5%)	59 (9%)
Headaches NEC Cluster Headache, Headache, Sinus Headache, Tension Headache	8 (5%)	125 (7%)	3 (7%)	69 (6%)	47 (5%)	12 (9%)	42 (7%)
Neurological Signs & Symptoms NEC Dizziness, Dysgeusia, Hypogeusia	2 (1%)	56 (3%)	0	31 (3%)	16 (2%)	9 (7%)	14 (2%)
Non-Site Specific Injuries NEC Arthropod Bite, Arthropod Sting, Contusion, Excoriation, Fall, Injury, Laceration, Road Traffic Accident, Soft Tissue Injury, Wound	3 (2%)	66 (4%)	1 (2%)	36 (3%)	21 (2%)	9 (7%)	21 (3%)

NEC = not elsewhere classified
Phase 2/3 studies included: TMX-00-004, TMX-01-005, C02-009, C02-010, and C02-021.
Cross-reference: Statistical Tables 3.1.2 and 3.3.2

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ON ORIGINAL

MedDRA High Level Term MedDRA Preferred Terms	Treatment Group n (%)						
	Placebo (N=172)	All Doses (N=1707)	40 mg QD (N=46)	80 mg QD (N=1180)	120 mg QD (N=876)	240 mg QD (N=134)	Allopurinol 300/100 mg QD (N=629)
Liver Function Analyses Alanine Aminotransferase Increased, Aspartate Aminotransferase Increased, Blood Bilirubin Increased, Gamma-Glutamyltransferase Increased, Hepatic Enzyme Increased, Liver Function Test Abnormal, Transaminases Increased	5 (3%)	85 (5%)	3 (7%)	47 (4%)	30 (3%)	6 (4%)	28 (4%)
Gastrointestinal & Abdominal Pains (Excl Oral & Throat) Abdominal Pain, Abdominal Pain Lower, Abdominal Pain Upper, Abdominal Tenderness, Gastrointestinal Pain	6 (3%)	53 (3%)	1 (2%)	27 (2%)	18 (2%)	8 (6%)	13 (2%)
Nausea & Vomiting Symptoms Nausea, Vomiting	5 (3%)	78 (5%)	0	44 (4%)	26 (3%)	8 (6%)	14 (2%)
Influenza Viral Infections Influenza	7 (4%)	90 (5%)	2 (4%)	47 (4%)	34 (4%)	7 (5%)	23 (4%)

NEC = not elsewhere classified
Phase 2/3 studies included: TMX-00-004, TMX-01-005, C02-009, C02-010, and C02-021.
Cross-reference: Statistical Tables 3.1.2 and 3.3.2

APPEARS THIS WAY
ON ORIGINAL

Reviewer's comments:

- Overall, it appears that the incidence of common AEs is the highest in 240 mg febuxostat group. Incidence of diarrhea, headaches NEC, neurological signs and symptoms NEC, gastrointestinal and abdominal pains, nausea and vomiting are highest in febuxostat 240 mg group.
- There is no difference in the incidence of AEs by MedDRA high level term between febuxostat 80 and 120 mg.
- There is slightly higher incidence of nausea, vomiting and diarrhea in febuxostat vs allopurinol groups (4% and 3% vs 2%, respectively). Incidence of upper respiratory infections (URI) and musculoskeletal and connective tissue symptoms are slightly higher in allopurinol group compared to either of febuxostat groups.

Table 20 (Sponsor's Table 3.2.b) Treatment-Emergent Adverse Events Occurring in 5% of Subjects in Any Treatment Group (Phase 2/3 Studies) - 4-Month Safety Update

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MedDRA High Level Term MedDRA Preferred Terms	Treatment Group n (%)						Allopurinol 300/100 mg QD (N=643)
	Placebo (N=172)	All Doses (N=1720)	40 mg QD (N=48)	80 mg QD (N=1225)	120 mg QD (N=932)	240 mg QD (N=134)	
Total Subjects with at Least 1 Adverse Event	116 (67%)	1317 (77%)	30 (63%)	870 (71%)	625 (67%)	98 (73%)	473 (74%)
Upper Respiratory Tract Infections Acute Sinusitis, Acute Tonsillitis, Chronic Sinusitis, Laryngitis, Nasopharyngitis, Pharyngitis, Rhinitis, Sinusitis, Tonsillitis, Upper Respiratory Tract Infection	25 (15%)	442 (26%)	6 (13%)	273 (22%)	166 (18%)	27 (20%)	138 (21%)
Musculoskeletal & Connective Tissue Signs & Symptoms NEC Back Pain, Buttock Pain, Chest Wall Pain, Dupuytren's Contracture, Flank Pain, Limb Discomfort, Muscle Spasms, Musculoskeletal Chest Pain, Musculoskeletal Discomfort, Musculoskeletal Pain, Musculoskeletal Stiffness, Neck Pain, Nodule on Extremity, Pain in Extremity	17 (10%)	245 (14%)	6 (13%)	139 (11%)	97 (10%)	14 (10%)	73 (11%)
Joint Related Signs & Symptoms Arthralgia, Joint Crepitation, Joint Effusion, Joint Range of Motion Decreased, Joint Stiffness, Joint Swelling, Temporomandibular Joint Syndrome	9 (5%)	233 (14%)	6 (13%)	144 (12%)	87 (9%)	7 (5%)	65 (10%)

NEC = not elsewhere classified

Studies included: TMX-00-004, TMX-01-005, C02-009, C02-010, and C02-021

Subjects who received study drug from more than 1 dose group are counted in each of those dose groups. Adverse events summarized were reported after the first dose of study drug and within 30 days of last dose of study drug. Subjects with 1 or more adverse events within a level of MedDRA term are counted only once in that level.

Cross-reference: Updated Statistical Tables 3.1.2 and 3.3.2

MedDRA High Level Term MedDRA Preferred Terms	Treatment Group n (%)						Allopurinol 300/100 mg QD (N=643)
	Placebo (N=172)	All Doses (N=1720)	40 mg QD (N=48)	80 mg QD (N=1225)	120 mg QD (N=932)	240 mg QD (N=134)	
Diarrhoea (Excl Infective) Diarrhoea	14 (8%)	173 (10%)	3 (6%)	87 (7%)	70 (8%)	18 (13%)	36 (6%)
Headaches NEC Cluster Headache, Headache, Sinus Headache, Tension Headache	8 (5%)	143 (8%)	3 (6%)	77 (6%)	57 (6%)	12 (9%)	45 (7%)
Neurological Signs & Symptoms NEC Dizziness, Dysgeusia, Hypogeusia, Tinel's Sign	2 (1%)	66 (4%)	0	37 (3%)	21 (2%)	9 (7%)	15 (2%)
Non-Site Specific Injuries NEC Animal Bite, Arthropod Bite, Arthropod Sting, Contusion, Excoriation, Fall, Foreign Body Trauma, Injury, Laceration, Road Traffic Accident, Soft Tissue Injury, Wound	3 (2%)	85 (5%)	1 (2%)	49 (4%)	28 (3%)	9 (7%)	22 (3%)
Liver Function Analyses ALT Increased, AST Increased, Blood Bilirubin Increased, GGT Increased, Hepatic Enzyme Abnormal, Hepatic Enzyme Increased, LFT Abnormal, Transaminases Increased	5 (3%)	106 (6%)	3 (6%)	56 (5%)	42 (5%)	6 (4%)	30 (5%)

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MedDRA High Level Term MedDRA Preferred Terms	Treatment Group n (%)						
	Placebo (N=172)	All Doses (N=1720)	40 mg QD (N=48)	80 mg QD (N=1225)	120 mg QD (N=932)	240 mg QD (N=134)	Allopurinol 300/100 mg QD (N=643)
Hyperlipidemia	0	21 (1%)	3 (6%)	14 (1%)	4 (<1%)	0	6 (<1%)
Hyperlipidemias							
Influenza Viral Infections	7 (4%)	99 (6%)	3 (6%)	53 (4%)	37 (4%)	7 (5%)	23 (4%)
Influenza							
Gastrointestinal & Abdominal Pains (Excl Oral & Throat)	6 (3%)	61 (4%)	1 (2%)	34 (3%)	19 (2%)	8 (6%)	15 (2%)
Abdominal Pain, Abdominal Pain Lower, Abdominal Pain Upper, Abdominal Tenderness, Gastrointestinal Pain							
Nausea & Vomiting Symptoms Nausea, Vomiting	5 (3%)	87 (5%)	0	48 (4%)	31 (3%)	8 (6%)	16 (2%)
Vascular Hypertensive Disorder NEC Hypertension	8 (5%)	96 (6%)	2 (4%)	59 (5%)	30 (3%)	6 (4%)	20 (3%)

Reviewer's comments:

- Results are similar to those observed in ISS
- The MedDRA preferred term of sinusitis was not previously included as one of the most commonly reported in the ISS, and the MedDRA preferred term of nausea is no longer included in the update as one of the most common adverse events.

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Table 21 (Sponsor's Table 3.3.4)
Most Frequently Reported Adverse Events for Subjects with Continuous Exposure in Phase 2/3 Studies (by preferred term)

MedDRA High Level Term/ Preferred Term	Febuxostat 40 - 240 mg			Allopurinol 300/100 mg		
	ISS	NEW	UPDATE	ISS	NEW	UPDATE
Total Number of Subjects	1392		1395	532		532
UPPER RESPIRATORY TRACT INFECTIONS	342 (25%)	82	383 (27%)	130 (24%)	2	131 (25%)
ACUTE SINUSITIS	0	0	0	1 (<1%)	0	1 (<1%)
ACUTE TONSILLITIS	1 (<1%)	0	1 (<1%)	0	0	0
CHRONIC SINUSITIS	0	0	0	0	1	1 (<1%)
LARYNGITIS	2 (<1%)	0	3 (<1%)	0	0	0
NASOPHARYNGITIS	157 (11%)	28	173 (12%)	46 (9%)	1	47 (9%)
PHARYNGITIS	7 (<1%)	2	8 (<1%)	2 (<1%)	0	3 (<1%)
RHINITIS	6 (<1%)	0	6 (<1%)	2 (<1%)	0	2 (<1%)
SINUSITIS	52 (4%)	15	64 (5%)	18 (3%)	0	18 (3%)
TONSILLITIS	1 (<1%)	0	1 (<1%)	0	0	0
UPPER RESPIRATORY TRACT INFECTION	149 (11%)	37	174 (12%)	72 (14%)	0	72 (14%)

Studies included: TNX-00-004, TNX-01-005, C02-009, C02-010, and C02-021. Continuous exposure summarizes data from subjects who received the same treatment (regardless of dose) in an extension study as in the previous study. For details see the statistics methods section of the ISS.
Febuxostat doses include: 40 mg, 80 mg, 120 mg, and 240 mg.
Adverse events summarized were reported after the first dose of study drug and within 30 days of the last dose of study drug.
Subjects with one or more adverse events within a level of the MedDRA term are counted only once in that level.
Most frequent events are those High Level Terms occurring in at least 5% (prior to rounding) of subjects in either the 'ISS' column or the 'UPDATE' column.
The 'NEW' column is the number of subjects with adverse events that were not included in the ISS.

MedDRA High Level Term/ Preferred Term	Febuxostat 40 - 240 mg			Allopurinol 300/100 mg		
	ISS	NEW	UPDATE	ISS	NEW	UPDATE
MUSCULOSKELETAL AND CONNECTIVE TISSUE SIGNS AND SYMPTOMS NEC	196 (13%)	52	225 (15%)	67 (13%)	3	70 (13%)
BACK PAIN	78 (4%)	26	99 (7%)	25 (5%)	3	28 (5%)
BUTTOCK PAIN	2 (<1%)	0	2 (<1%)	0	0	0
CHEST WALL PAIN	6 (<1%)	1	7 (<1%)	1 (<1%)	0	1 (<1%)
DUPUYTREN'S CONTRACTURE	1 (<1%)	0	1 (<1%)	0	0	0
FLANK PAIN	4 (<1%)	1	5 (<1%)	2 (<1%)	0	3 (<1%)
LIMB DISCOMFORT	0	0	0	1 (<1%)	0	1 (<1%)
MUSCLE SPASMS	9 (<1%)	2	10 (<1%)	2 (<1%)	0	2 (<1%)
MUSCULOSKELETAL CHEST PAIN	1 (<1%)	0	1 (<1%)	0	0	0
MUSCULOSKELETAL DISCOMFORT	1 (<1%)	1	2 (<1%)	0	0	0
MUSCULOSKELETAL PAIN	1 (<1%)	0	1 (<1%)	0	0	0
MUSCULOSKELETAL STIFFNESS	9 (<1%)	4	12 (<1%)	7 (1%)	0	7 (1%)
NECK PAIN	11 (<1%)	3	13 (<1%)	6 (1%)	0	6 (1%)
NEURALE CN EXTREMITY	1 (<1%)	0	1 (<1%)	0	0	0
PAIN IN EXTREMITY	93 (7%)	17	105 (8%)	31 (6%)	0	31 (6%)
JOINT RELATED SIGNS AND SYMPTOMS	153 (10%)	50	201 (14%)	57 (11%)	3	50 (10%)
ARTHRALGIA	145 (10%)	46	175 (12%)	47 (9%)	3	50 (9%)
JOINT CREPITATION	1 (<1%)	0	1 (<1%)	0	0	0
JOINT EFFUSION	5 (<1%)	0	5 (<1%)	2 (<1%)	0	2 (<1%)
JOINT RANGE OF MOTION DECREASED	3 (<1%)	0	3 (<1%)	0	0	0
JOINT STIFFNESS	12 (<1%)	1	13 (<1%)	4 (<1%)	0	4 (<1%)
JOINT SWELLING	13 (<1%)	4	16 (1%)	5 (<1%)	0	5 (<1%)
TEMPOROMANDIBULAR JOINT SYNDROME	1 (<1%)	0	1 (<1%)	0	0	0
DIARRHOEA (EXCL INFECTIVE)	145 (10%)	16	157 (11%)	33 (6%)	1	34 (6%)
DIARRHOEA	145 (10%)	16	157 (11%)	33 (6%)	1	34 (6%)
HEADACHES NEC	117 (8%)	16	126 (9%)	42 (8%)	1	43 (8%)
CLUSTER HEADACHE	1 (<1%)	0	1 (<1%)	0	0	0
HEADACHE	111 (8%)	15	120 (9%)	42 (8%)	1	43 (8%)
SINUS HEADACHE	5 (<1%)	2	6 (<1%)	1 (<1%)	0	1 (<1%)
TENSION HEADACHE	4 (<1%)	1	4 (<1%)	0	0	0
LIVER FUNCTION ANALYSES	63 (4%)	15	96 (7%)	27 (5%)	0	27 (5%)
ALANINE AMINO-TRANSFERASE INCREASED	22 (2%)	7	30 (2%)	6 (1%)	0	6 (1%)
ASPARTATE AMINOTRANSFERASE INCREASED	17 (1%)	5	22 (2%)	5 (<1%)	0	5 (<1%)
BLOOD BILIRUBIN INCREASED	4 (<1%)	0	4 (<1%)	1 (<1%)	0	1 (<1%)
GAMMA-GLUTAMYLTRANSFERASE INCREASED	2 (<1%)	1	3 (<1%)	0	0	0
HEPATIC ENZYME ABNORMAL	0	0	1 (<1%)	0	0	0
HEPATIC ENZYME INCREASED	37 (3%)	2	37 (3%)	13 (2%)	0	13 (2%)
LIVER FUNCTION TEST ABNORMAL	27 (2%)	5	32 (2%)	8 (2%)	0	8 (2%)
TRANSAMINASES INCREASED	1 (<1%)	0	1 (<1%)	0	0	0
INFLUENZA VIRAL INFECTIONS	62 (4%)	11	68 (5%)	22 (4%)	0	22 (4%)
INFLUENZA	62 (4%)	11	68 (5%)	22 (4%)	0	22 (4%)
NAUSEA AND VOMITING SYMPTOMS	76 (5%)	6	82 (6%)	14 (2%)	1	15 (3%)
NAUSEA	64 (5%)	3	66 (5%)	11 (2%)	1	12 (2%)
VOMITING	22 (2%)	3	27 (2%)	3 (<1%)	0	3 (<1%)
VASCULAR HYPERTENSIVE DISORDERS NEC	56 (4%)	26	82 (6%)	17 (3%)	1	18 (3%)
HYPERTENSION	56 (4%)	26	82 (6%)	17 (3%)	1	18 (3%)

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MedDRA High Level Term/ Preferred Term	Febuxostat 40 - 240 mg			Allopurinol 300/100 mg		
	ISS	NEM	UPDATE	ISS	NEM	UPDATE
NON-SITE SPECIFIC INJURIES NEC	65 (5%)	13	77 (6%)	21 (3%)	1	22 (4%)
ANIMAL BITE	0	1	1 (<1%)	0	0	0
ARTHROPOD BITE	7 (<1%)	2	9 (<1%)	1 (<1%)	0	1 (<1%)
ARTHROPOD STING	3 (<1%)	0	3 (<1%)	1 (<1%)	0	1 (<1%)
CONUSION	20 (1%)	3	24 (<2%)	9 (1%)	0	9 (<2%)
EXCORIATION	11 (<1%)	3	14 (<1%)	4 (<1%)	0	4 (<1%)
FALL	14 (1%)	3	17 (<1%)	1 (<1%)	1	2 (<1%)
FOREIGN BODY TRAUMA	0	1	1 (<1%)	0	0	0
INJURY	3 (<1%)	0	3 (<1%)	3 (<1%)	0	3 (<1%)
LACERATION	1 (<1%)	0	1 (<1%)	1 (<1%)	0	2 (<1%)
ROAD TRAFFIC ACCIDENT	8 (<1%)	0	8 (<1%)	1 (<1%)	0	1 (<1%)
SOFT TISSUE INJURY	2 (<1%)	0	2 (<1%)	2 (<1%)	0	2 (<1%)
WOUND	4 (<1%)	0	4 (<1%)	0	0	0

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The 10 most commonly reported treatment-emergent adverse events during febuxostat 40-240 mg QD treatment included the following MedDRA preferred terms: nasopharyngitis, upper respiratory tract infection, diarrhea, arthralgia, headache, pain in extremity, influenza, back pain, nausea, and hypertension.

The 11 most commonly reported treatment-emergent adverse events during allopurinol 300/100 mg QD treatment included the following MedDRA preferred terms: upper respiratory tract infection, arthralgia, nasopharyngitis, headache, diarrhea, pain in extremity, back pain, influenza, sinusitis, hypertension, and constipation.

7.1.3.4 Common adverse event tables

See also Section 7.1.3.3

Table 22 (Sponsor's Table 3.7b, ISS) Time of Onset of Most Frequent Adverse Events in Subjects with Continuous Exposure (Phase 2/3 Studies)

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MedDRA High Level Term	Time Interval n (%)									
	1-<7 days	7 days-<1 month	1-<3 months	3-<6 months	6-<9 months	9-<12 months	12-<15 months	15-<18 months	18-<24 months	24-<36 months
Treatment-Emergent Adverse Events										
Number of Subjects Treated										
Febuxostat 40-240 mg QD ^a	1392	1366	1367	1062	928	634	438	310	203	71
Allopurinol 300/100 mg QD	522	524	499	455	420	211	183	7	NA	NA
Total Subjects with at Least 1 Adverse Event										
Febuxostat 40-240 mg QD ^a	218 (16%)	384 (28%)	522 (41%)	471 (44%)	339 (37%)	265 (32%)	152 (35%)	83 (27%)	46 (21%)	33 (46%)
Allopurinol 300/100 mg QD	59 (11%)	147 (28%)	226 (44%)	223 (49%)	133 (32%)	81 (38%)	14 (8%)	1 (14%)	NA	NA
Upper Respiratory Tract Infections										
Febuxostat 40-240 mg QD ^a	8 (<1%)	53 (4%)	78 (6%)	102 (9%)	76 (8%)	43 (7%)	33 (7%)	16 (5%)	18 (9%)	5 (7%)
Allopurinol 300/100 mg QD	3 (<1%)	20 (4%)	39 (8%)	50 (11%)	24 (6%)	17 (8%)	3 (2%)	0	NA	NA
Musculoskeletal & Connective Tissue Signs & Symptoms NEC										
Febuxostat 40-240 mg QD ^a	11 (<1%)	33 (2%)	57 (5%)	52 (5%)	29 (3%)	14 (2%)	16 (4%)	5 (2%)	2 (<1%)	7 (10%)
Allopurinol 300/100 mg QD	2 (<1%)	11 (2%)	23 (5%)	20 (4%)	10 (2%)	10 (5%)	1 (<1%)	1 (14%)	NA	NA
Joint Related Signs & Symptoms										
Febuxostat 40-240 mg QD ^a	5 (<1%)	30 (2%)	53 (4%)	39 (4%)	34 (4%)	19 (3%)	14 (3%)	7 (2%)	2 (<1%)	1 (1%)
Allopurinol 300/100 mg QD	7 (1%)	10 (2%)	15 (3%)	20 (4%)	9 (2%)	7 (2%)	2 (1%)	0	NA	NA
Diarrhoea (Excl Infective)										
Febuxostat 40-240 mg QD ^a	38 (3%)	33 (2%)	38 (3%)	25 (2%)	8 (<1%)	6 (<1%)	7 (2%)	2 (<1%)	2 (<1%)	0
Allopurinol 300/100 mg QD	11 (2%)	8 (2%)	7 (1%)	3 (<1%)	3 (<1%)	1 (<1%)	0	0	NA	NA
Headaches NEC										
Febuxostat 40-240 mg QD ^a	22 (2%)	23 (2%)	34 (3%)	13 (1%)	18 (2%)	10 (2%)	12 (3%)	3 (<1%)	6 (3%)	2 (3%)
Allopurinol 300/100 mg QD	8 (2%)	10 (2%)	11 (2%)	16 (3%)	5 (1%)	1 (<1%)	0	0	NA	NA
Influenza Viral Infections										
Febuxostat 40-240 mg QD ^a	3 (<1%)	6 (<1%)	19 (1%)	28 (3%)	11 (1%)	9 (1%)	7 (2%)	3 (<1%)	3 (1%)	0
Allopurinol 300/100 mg QD	6	2 (<1%)	7 (1%)	8 (2%)	2 (<1%)	3 (1%)	1 (<1%)	0	NA	NA

NEC = not elsewhere classified

Studies included: TMX-00-004, TMX-01-005, C02-009, C02-010, and C02-021.

Most frequent treatment-emergent adverse events include only those high level terms that occurred in ≥2% of subjects in either treatment group and treatment-related adverse events include only those high level terms that occurred in ≥2% of subjects in either treatment group.

a Febuxostat doses included 40, 80, 120, and 240 mg QD.

Cross-reference: Statistical Tables 3.14.2 and 3.15.2

MedDRA High Level Term	Time Interval n (%)									
	1-<7 days	7 days-<1 month	1-<3 months	3-<6 months	6-<9 months	9-<12 months	12-<15 months	15-<18 months	18-<24 months	24-<36 months
Treatment-Related Adverse Events										
Liver Function Analyses										
Febuxostat 40-240 mg QD ^a	6 (<1%)	18 (1%)	27 (2%)	21 (2%)	15 (2%)	3 (<1%)	1 (<1%)	0	0	0
Allopurinol 300/100 mg QD	1 (<1%)	8 (2%)	9 (2%)	6 (1%)	2 (<1%)	0	0	0	NA	NA
Nausea & Vomiting Symptoms										
Febuxostat 40-240 mg QD ^a	13 (<1%)	14 (1%)	20 (2%)	11 (1%)	5 (<1%)	5 (<1%)	5 (1%)	1 (<1%)	1 (<1%)	0
Allopurinol 300/100 mg QD	4 (<1%)	4 (<1%)	3 (<1%)	4 (<1%)	0	0	0	0	NA	NA
Treatment-Related Adverse Events										
Total Subjects with at Least 1 Adverse Event										
Febuxostat 40-240 mg QD ^a	96 (7%)	95 (7%)	113 (9%)	62 (5%)	43 (5%)	17 (3%)	14 (3%)	8 (3%)	3 (1%)	1 (1%)
Allopurinol 300/100 mg QD	26 (5%)	39 (7%)	28 (6%)	25 (5%)	13 (3%)	3 (1%)	0	0	NA	NA
Diarrhoea (Excl Infective)										
Febuxostat 40-240 mg QD ^a	24 (2%)	13 (<1%)	13 (1%)	3 (<1%)	3 (<1%)	1 (<1%)	1 (<1%)	0	1 (<1%)	0
Allopurinol 300/100 mg QD	8 (1%)	3 (<1%)	2 (<1%)	1 (<1%)	0	0	0	0	NA	NA
Liver Function Analyses										
Febuxostat 40-240 mg QD ^a	2 (<1%)	9 (<1%)	17 (1%)	13 (1%)	13 (1%)	3 (<1%)	0	0	0	0
Allopurinol 300/100 mg QD	1 (<1%)	6 (1%)	6 (1%)	5 (1%)	1 (<1%)	0	0	0	NA	NA
Headaches NEC										
Febuxostat 40-240 mg QD ^a	10 (<1%)	8 (<1%)	8 (<1%)	3 (<1%)	1 (<1%)	0	3 (<1%)	0	1 (<1%)	1 (1%)
Allopurinol 300/100 mg QD	7 (1%)	3 (<1%)	1 (<1%)	2 (<1%)	0	0	0	0	NA	NA

NEC = not elsewhere classified

Studies included: TMX-00-004, TMX-01-005, C02-009, C02-010, and C02-021.

Most frequent treatment-emergent adverse events include only those high level terms that occurred in ≥2% of subjects in either treatment group and treatment-related adverse events include only those high level terms that occurred in ≥2% of subjects in either treatment group.

a Febuxostat doses included 40, 80, 120, and 240 mg QD.

Cross-reference: Statistical Tables 3.14.2 and 3.15.2

7.1.3.5 Identifying common and drug-related adverse events

Table 23 (Sponsor's Table 1.5b, ISS)
Definitions for Investigator Assessment of Adverse Event Relationship to Study Drug

Rating	Definition
Definite	The adverse event followed a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug) and satisfied any of the following: reappearance of similar reaction by repeated exposure (re-challenge), positive results in drug sensitivity tests (lymphocyte blastoid transformation test, skin test, etc.), or toxic levels of the drug in the blood or other body fluids.
Probable	The adverse event followed a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug or rechallenge), and the possibilities of factors other than the drug, such as underlying disease, concomitant drugs or concurrent treatment, were excluded.
Possible	The adverse event followed a reasonable temporal sequence from administration of the drug (including the course after withdrawal of the drug or rechallenge), and the possibility of drug involvement could not be excluded, eg, existence of similar reports attributable to the suspected drug, its analog, or its pharmacological effect. However, other factors such as underlying disease complications, concomitant drugs, or concurrent treatment were presumable.
Unlikely	The adverse event had an improbable temporal sequence from administration of the drug, or it could have been reasonably explained by other factors, including underlying disease complications, concomitant drugs, or concurrent treatment.
Not Related	The adverse event had no temporal sequence from administration of the drug, or it could be reasonably explained by other factors, including underlying disease complications, concomitant drugs, or concurrent treatment.

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The overall incidence of treatment-related adverse events was similar in the febuxostat 40-240 mg QD and allopurinol 300/100 mg QD groups (25% and 20%, respectively).

Based on the investigator's assessments, the 10 most commonly reported treatment-related adverse events during febuxostat 40-240 mg QD treatment included the following MedDRA preferred terms: diarrhoea, headache, nausea, hepatic enzyme increased, liver function test abnormal, constipation, dizziness, dyspepsia, arthralgia, and pain in extremity.

The 13 most commonly reported treatment-related adverse events during allopurinol 300/100 mg QD treatment included the following MedDRA preferred terms: diarrhoea, headache, hepatic enzyme increased, constipation, arthralgia, liver function test abnormal, pain in extremity, rash erythematous, alanine aminotransferase increased, dyspepsia, aspartate aminotransferase increased, tinnitus, and nausea. Due to similar reporting rates for certain preferred terms, 13 rather than 10 adverse events are presented.

Table 24 (Sponsor's Table 3.2f, ISS) Treatment-Related Adverse Events Occurring in $\geq$ 2% of Subjects in Either Treatment Group in Subjects with Continuous Exposure (Phase 2/3 Studies)

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MedDRA High Level Term MedDRA Preferred Terms	Treatment Group n (%)	
	Febuxostat 40-240 mg QD (N=1392)	Allopurinol 300/100 mg QD (N=532)
Total Subjects with at Least 1 Adverse Event	352 (25%)	104 (20%)
Diarrhoea (Excl Infective)	55 (4%)	12 (2%)
Diarrhoea		
Liver Function Analyses	53 (4%)	19 (4%)
Alanine Aminotransferase Increased, Aspartate Aminotransferase Increased, Blood Bilirubin Increased, Gamma-Glutamyltransferase Increased, Hepatic Enzyme Increased, Liver Function Test Abnormal, Transaminases Increased		
Headaches NEC	35 (3%)	12 (2%)
Headache		
Nausea & Vomiting Symptoms	29 (2%)	5 (<1%)
Nausea, Vomiting		

NEC = not elsewhere classified
Studies included: TMX-00-004, TMX-01-005, C02-009, C02-010, and C02-021.
Cross-reference: Statistical Tables 3.2.4 and 3.4.4

Reviewer's comment:

- *In this reviewer's opinion, the events listed in the above table can reasonably be considered drug-related.*
- *Since febuxostat and allopurinol have similar mechanism of action, it would be reasonable to assume that side effects of those two drugs would be manifested in the same organ systems, such as gastro-intestinal, renal, hepatic, skin; however it does not mean that magnitude of toxicity is also expected to be the same*
- *Of note, most patients in the development program were on multiple medications due to different underlying conditions, thus making it difficult to ascertain the causality*

7.1.3.6 Additional analyses and explorations

None

7.1.4 Less Common Adverse Events

As already discussed in Section 7.1.1 (Deaths), there were two deaths due to retroperitoneal hemorrhage in patients on warfarin due to increased INR. In a formal drug-drug interaction study of multiple doses of febuxostat 120 mg, the Sponsor concluded that there were no pharmacokinetic and pharmacodynamic interactions between febuxostat and warfarin. However, 9 out of 25 patients (4 in placebo group and 5 in febuxostat group) discontinued the study prior to blood sampling because they had increased INR and required Vit. K. It is the loss of these subjects to data collection that is the most troubling in that it had the net effect of censoring the data.

In addition to that, 2 discontinuations from the study due to serious AE listing increased INR (5.6 and 6) in patients on coumadin were identified.

Reviewer's conclusion:

- Based on above findings, this reviewer concludes that the conclusion from the Study C03-057 might be misleading

b(4)

7.1.5 Laboratory Findings

7.1.5.1 Overview of laboratory testing in the development program

A clinical laboratory safety evaluation was performed at specified visits. Laboratory reports were signed and dated by the principal investigator or subinvestigator indicating that the report had been reviewed and any abnormalities had been assessed for clinical significance. A clinically significant laboratory abnormality that had been verified by retesting was to be followed until the abnormality returned to an acceptable level or a satisfactory explanation had been obtained.

The laboratory safety evaluations to be performed during the course of the studies are presented in Table 25.

Table 25 (Sponsor's Table 1.5c, ISS) Laboratory Tests

Hematology Tests	Urinalysis
White blood cell (WBC) count with differential	Color*
Hemoglobin	Bilirubin*
Hematocrit	Urobilinogen*
Mean corpuscular hemoglobin (MCH)	Leukocyte esterase*
Mean corpuscular hemoglobin concentration (MCHC)	Specific gravity
Mean corpuscular volume (MCV)	Protein
Platelet count	Nitrite
Reticulocyte count	Ketones
Prothrombin time (PT)	Glucose
Partial thromboplastin time (PTT)	pH
Red blood cell (RBC) count	Microscopic examination for RBCs, WBCs, epithelial cells*, yeast*, bacteria*, casts, and crystals
	Occult blood*
Chemistry Tests	
Alanine aminotransferase/serum glutamate pyruvate transaminase (ALT/SGPT)	Lactic dehydrogenase (LDH)
Albumin	Magnesium
Alkaline phosphatase	Phosphorus
Amylase	Potassium
Aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT)	Serum urate
Bicarbonate	Sodium
Blood urea nitrogen (BUN)	Total bilirubin
Calcium	Total cholesterol
Chloride	Total protein
Creatinine	Triglycerides
Glucose	
Thyroid Function Tests	
Thyroid stimulating hormone (TSH)	Total thyroxine (T ₄)
Total triiodothyronine (T ₃)	Free thyroxine (FT ₄)

* Study C02-009 only.

Best Possible Copy

In the Phase 3 controlled studies, all female subjects of child-bearing potential had a pregnancy test prior to dosing and at protocol-specified timepoints.

7.1.5.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The Sponsor performed analyses of laboratory values over time, which focuses on mean change from baseline at Weeks 28 and 52 as well as individual subject changes. The analyses encompass both shift analyses and potentially concerning laboratory values analyses. It included summaries of mean changes from baseline for hematology, chemistry, endocrinology, and urinalysis parameters in the Phase 1, 2, and 3 studies.

7.1.5.3 Standard analyses and explorations of laboratory data

7.1.5.3.1 *Analyses focused on measures of central tendency*

Hematology

Phase 3 Controlled Studies

Statistically significant differences were observed between the febuxostat 80 mg QD and allopurinol 300/100 mg QD treatment groups for the mean change from baseline to the Week 28 and/or Week 52 Visits in the following hematology parameters: **RBC, MCV, MCH, lymphocytes, and eosinophils.**

Statistically significant differences were also observed between the febuxostat 120 mg QD and allopurinol 300/100 mg QD treatment groups for the mean change from baseline to the Week 28 and/or Week 52 Visits in the following hematology parameters: **RBC, MCV, MCH, and platelet count (Table 26)**

Additionally, a statistically significant difference was observed between the febuxostat 80 mg QD and 120 mg QD treatment groups for the mean change from baseline to the Week 28 Visit in **MCHC and lymphocytes (Table 26)**. Sporadic statistically significant treatment group differences were observed at various other timepoints for these parameters. None of the treatment differences was considered clinically significant.

Across febuxostat treatment groups and at multiple timepoints, the mean RBC count increased and MCV and MCH decreased slightly. For some treatment groups and timepoints, these changes were statistically significant. However, the magnitude was small and there were no matching statistically significant changes in hemoglobin or hematocrit, and no consistent change in MCHC, indicating that the changes are of no clinical significance. There was a consistent but medically unimportant increase in platelet counts and decrease in lymphocytes across all

treatment groups. Changes in the other parameters were inconsistent, rarely statistically significant, medically unimportant, and showed no recognizable pattern.

There was no new information included with 4- months' safety update.

Table 26 (Sponsor's Table 4.1a, ISS)
Statistically Significant Treatment Group Differences in Mean Change from Baseline to the Week 28 and/or Week 52 Visits - Hematology Parameters (Phase 3 Controlled Studies)

Hematology Parameter (unit)	Placebo			Febuxostat 80 mg QD			Febuxostat 120 mg QD			Febuxostat 240 mg QD			Allopurinol 300/100 mg QD		
	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)
RBC (x10⁹/mL)															
Baseline	122	5.003	0.4184	491	4.992	0.4522	491	5.030	0.4128	121	4.893	0.3809	492	4.980	0.4326
Mean Δ at Week 28	93	0.109	0.2805	344	0.075 ^a	0.2713	343	0.066 ^a	0.2657	80	0.069	0.2447	403	0.094	0.2868
MCV (fL)															
Baseline	122	91.01	5.151	491	89.72	5.528	491	89.39	5.078	121	91.63	4.835	492	89.60	5.103
Mean Δ at Week 28	93	-3.61	3.103	344	-0.29	4.473	341	-0.82 ^a	4.249	80	-3.98	2.638	402	0.33	4.606
Mean Δ at Week 52				157	-0.41 ^a	2.604	142	-0.59 ^a	2.913				175	0.86	3.332
MCH (pg)															
Baseline	122	30.61	1.669	491	30.33	2.120	491	30.32	1.894	121	30.59	1.592	492	30.38	1.925
Mean Δ at Week 28	93	-0.13	0.969	344	-0.29 ^a	1.023	343	-0.21 ^a	0.990	80	-0.04	0.947	403	0.09	1.015
Mean Δ at Week 52				157	-0.29 ^a	0.929	142	-0.23 ^a	1.036				175	0.23	1.311
MCHC (g/dL)															
Baseline	122	33.62	1.242	491	33.81	1.459	491	33.93	1.369	121	33.34	1.166	492	33.93	1.410
Mean Δ at Week 28	93	1.22	1.374	344	-0.21 ^a	1.817	341	0.09	1.724	80	1.48	1.263	402	-0.05	1.781
Platelet Count (x10⁹/mL)															
Baseline	122	245.8	60.46	490	251.2	65.65	490	244.8	58.62	121	257.0	60.35	489	250.9	62.52
Mean Δ at Week 28	93	-18.5	43.61	342	9.8	-41.83	341	14.9 ^a	-43.97	79	28.0	38.24	400	6.1	47.01
Lymphocytes (x10⁹/mL)															
Baseline	122	2.133	0.5935	491	2.072	0.6383	491	2.216	0.7286	121	2.078	0.7376	492	2.155	0.6516
Mean Δ at Week 28	93	-0.155	0.4451	344	0.002 ^{a,m}	0.3967	343	-0.082	0.4909	80	-0.023	0.4248	403	-0.028	0.4531
Eosinophils (x10⁹/mL)															
Baseline	122	0.189	0.1716	491	0.171	0.1079	491	0.182	0.1193	121	0.160	0.1467	492	0.188	0.1537
Mean Δ at Week 52				157	0.006 ^a	0.1045	142	-0.009	0.1129				175	-0.028	0.1233

Phase 3 studies included: C02-009 and C02-010.

Note: Study C02-009 was a 28-week trial that included placebo and febuxostat 240 mg QD treatment groups. Thus, changes to Week 52 for these 2 groups of subjects were not relevant and no data are displayed.

a Statistically significant difference versus allopurinol 300/100 mg QD (p<0.05) using ANOVA.

m Statistically significant difference versus febuxostat 120 mg QD (p<0.05) using ANOVA.

Cross-reference: Statistical Table 4.1.2.1

Continuous Exposure in Phase 2/3 Studies

Among subjects with continuous exposure in the Phase 2/3 studies, small mean changes from baseline to each visit were identified for various hematology parameters that were similar across treatment groups. Each of the mean changes from baseline was not considered clinically significant.

Findings in safety update were similar to those in the original ISS analysis.

Reviewer's comments:

- Summary Table 23 from phase 3 trials presents only those parameters that showed statistically significant differences between treatment groups
- Changes in values of different parameters at weeks 28 and 52 are varied in direction (increase/decrease) and magnitude across the groups
- There was no summary table for pooled data from all phase 2/3 trials

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Chemistry

Phase 3 Controlled Studies

Statistically significant differences were observed between the febuxostat 80 mg QD and allopurinol 300/100 mg QD treatment groups for the mean change from baseline to the Week 28 and/or Week 52 Visits in the following chemistry parameters: **total bilirubin, alkaline phosphatase, ALT, and total cholesterol.**

Statistically significant differences were also observed between the febuxostat 120 mg QD and allopurinol 300/100 mg QD treatment groups for the mean change from baseline to the **Week 28 and/or Week 52** Visits in the following chemistry parameters: **sodium, creatinine, inorganic phosphorus, total bilirubin, alkaline phosphatase, AST, ALT, total cholesterol, and magnesium (Table 27).**

Additionally, statistically significant differences were observed between the febuxostat 80 mg QD and 120 mg QD treatment groups for the mean change from baseline to the Week 28 Visit in **alkaline phosphatase and LDH** and to Week 52 in **inorganic phosphorus.**

Sporadic statistically significant treatment group differences were observed at various other timepoints for these parameters.

Of note, no statistically significant treatment differences were observed for change from baseline to Week 28 in measured Cl_{cr} . However, the mean change to Week 28 in measured Cl_{cr} was greater in the febuxostat 240 mg QD treatment group (-17.2 mL/minute) compared to the other treatment groups (-6.9 to 2.0 mL/minute). This higher decrease was due to 1 subject having a serum creatinine of 0.1 mg/dL at baseline, which resulted in a baseline measured Cl_{cr} of 1053 mL/minute. The baseline serum creatinine result is a laboratory error, as it is not compatible with life. The subject's serum creatinine values ranged from 0.7 to 0.9 mg/dL at other visits, and the subject had a measured Cl_{cr} of 133 mL/minute at the end of the study (C02-009 CSR). This subject subsequently had a normal serum creatinine and normal measured Cl_{cr} at Week 28, which resulted in a high decrease in Cl_{cr} over time. In addition, no differences were noted between treatment groups for the shift analysis of measured Cl_{cr} .

There were no consistent statistically significant changes in serum electrolytes (ie, **sodium, potassium, chloride, bicarbonate), glucose, BUN, or creatinine.** Changes were sporadic at different timepoints and varied in direction (increase/decrease) and magnitude.

Changes in **total bilirubin, LDH, and alkaline phosphatase** were inconsistent, and only sporadically statistically significant. However, mean increases in **AST and ALT** were observed in all treatment groups at the majority of timepoints. Although sporadically statistically significant, the magnitude of change was similar across treatment groups.

There were no consistent statistically significant changes in **calcium, phosphorus, magnesium, or total cholesterol.** Although sporadically statistically significant, the

magnitude of change was similar across treatment groups.

There was no new information submitted with safety update for phase 3 trials.

Table 27 (Sponsor's Table 4.1b, ISS)
Statistically Significant Treatment Group Differences in Mean Change from Baseline to the Week 28 and/or Week 52 Visits - Chemistry Parameters (Phase 3 Controlled Studies)

Chemistry Parameter (unit)	Placebo			Febuxostat 80 mg QD			Febuxostat 120 mg QD			Febuxostat 240 mg QD			Allopurinol 300/100 mg QD		
	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)
Sulfur (mg/dL)															
Baseline	129	141.5	2.26	508	142.5	2.74	586	142.2	2.68	127	142.2	2.31	506	142.4	2.33
Mean Δ at Week 28	97	0.1	3.07	352	-1.0	2.85	347	-0.6*	3.44	83	-0.4	2.70	409	-1.1	2.91
Creatinine (mg/dL)															
Baseline	129	0.99	0.271	508	1.02	0.241	586	1.03	0.223	127	1.04	0.274	506	1.02	0.228
Mean Δ at Week 52				160	-0.03	0.132	145	-0.05*	0.143				178	-0.02	0.152
Inorganic Phosphorus (mg/dL)															
Baseline	129	3.42	0.593	508	3.42	0.594	586	3.45	0.540	127	3.45	0.626	506	3.43	0.523
Mean Δ at Week 52				160	0.05**	0.550	144	-0.09*	0.516				178	0.05	0.503
Total Bilirubin (mg/dL)															
Baseline	129	0.781	0.3281	508	0.560	0.2766	586	0.593	0.3220	127	0.583	0.2953	506	0.548	0.2686
Mean Δ at Week 52				160	-0.016*	0.2059	144	-0.019*	0.2639				178	0.041	0.2094
Alkaline Phosphatase (IU/L)															
Baseline	129	76.6	19.86	508	75.5	24.79	586	76.6	21.12	127	78.0	23.70	506	77.9	20.77
Mean Δ at Week 28	97	1.0	12.96	351	1.1**	12.64	347	-1.2*	11.51	83	-0.2	10.86	409	3.4	11.38
Mean Δ at Week 52				160	-0.3*	13.27	144	-0.1*	11.23				178	2.9	11.05

Phase 3 studies included: C02-009 and C02-010.

Note: Study C02-009 was a 28-week trial that included placebo and febuxostat 240 mg QD treatment groups. Thus, changes to Week 52 for these 2 groups of subjects were not relevant and no data are displayed.

a Statistically significant difference versus allopurinol 300/100 mg QD (p<0.05) using ANOVA.

m Statistically significant difference versus febuxostat 120 mg QD (p<0.05) using ANOVA.

Cross-reference: Statistical Table 4.1.2.2

Chemistry Parameter (unit)	Placebo			Febuxostat 80 mg QD			Febuxostat 120 mg QD			Febuxostat 240 mg QD			Allopurinol 300/100 mg QD		
	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)
AST (IU/L)															
Baseline	129	26.0	7.83	508	27.5	12.42	586	27.0	10.94	127	26.2	9.63	506	26.3	11.83
Mean Δ at Week 28	96	1.3	8.82	348	1.8	10.03	342	3.2*	18.35	82	1.9	9.83	406	0.3	10.94
PdET (IU/L)															
Baseline	129	30.5	14.31	508	33.2	19.05	586	33.2	16.30	127	30.4	16.38	506	31.9	15.71
Mean Δ at Week 28	97	2.0	12.92	350	3.4*	14.87	346	4.7*	19.63	83	4.9	14.51	409	-0.4	13.78
LDH (IU/L)															
Baseline	129	162.0	30.42	508	162.1	40.74	586	158.9	31.24	126	160.1	31.97	506	160.0	32.01
Mean Δ at Week 28	96	0.3	21.76	344	-2.8**	26.06	340	1.7	30.99	82	-3.5	23.11	403	-1.3	23.02
Total Cholesterol (mg/dL)															
Baseline	129	207.9	41.35	508	206.5	42.95	586	204.2	41.76	127	194.6	40.46	506	208.5	42.18
Mean Δ at Week 28	97	4.1	34.45	352	0.4*	34.69	347	3.4*	30.89	83	8.5	34.01	409	-5.2	33.52
Magnesium (mEq/L)															
Baseline	129	1.613	0.1335	508	1.611	0.1487	586	1.618	0.1479	127	1.625	0.1651	506	1.607	0.1335
Mean Δ at Week 28	97	0.049	0.1388	352	0.037	0.1457	347	0.020*	0.1375	83	-0.000	0.1476	409	0.046	0.1449

Continuous Exposure in Phase 2/3 Studies

Among subjects with continuous exposure in the Phase 2/3 studies, small mean changes from baseline to each visit were identified for various chemistry parameters that were similar across treatment groups. Each of the mean changes from baseline was not considered clinically significant.

Reviewer's comments:

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- **Summary Table 27 for phase 3 trials presents only those parameters that showed statistically significant differences between treatment groups**
- **There was no summary table for pooled data from all phase 2/3 trials**
- **Changes in values of different parameters at weeks 28 and 52 are varied in direction (increase/decrease) and magnitude across the groups**

Endocrinology

Phase 3 Controlled Studies

A statistically significant difference was observed between the febuxostat 80 mg QD and 120 mg QD treatment groups for the mean change from baseline to Week 52 in FT₄ (Table 28). A statistically significant difference was also observed between the febuxostat 80 mg QD and allopurinol 300/100 mg QD treatment groups for the mean change from baseline to Week 28 in TSH. Additionally, sporadic statistically significant treatment group differences were observed at various other timepoints for this parameter.

No statistically significant treatment group differences were observed in the analysis of mean change from baseline for total T₄ or total T₃. Statistically significant changes from baseline to the Week 28 and Week 52 Visits within treatment groups were found for some endocrine laboratory values. The mean changes from baseline were small.

Table 28 (Sponsor's Table 4.1c, ISS)
Statistically Significant Treatment Group Differences in Mean Change from Baseline to the Week 28 and/or Week 52 Visits - Endocrinology Parameters (Phase 3 Controlled Studies)

Endocrinology Parameter (unit)	Placebo			Febuxostat 80 mg QD			Febuxostat 120 mg QD			Febuxostat 240 mg QD			Allopurinol 300/100 mg QD		
	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)
FT ₄ (ng/dL)															
Baseline	168	1.01	0.148	401	1.00	0.138	393	1.02	0.144	97	1.02	0.154	432	1.01	0.132
Mean Δ at Week 52				154	-0.03 ^m	0.145	144	-0.06	0.128				171	-0.05	0.115
TSH (mIU/mL)															
Baseline	168	1.855	0.9319	402	2.507	7.2487	400	1.916	1.2130	96	1.970	1.2607	453	1.956	2.3048
Mean Δ at Week 28	97	-0.049	0.7287	172	-1.039 ^a	10.3046	192	0.082	0.8381	80	-0.017	0.8619	224	0.079	1.0410

Phase 3 studies included: C02-009 and C02-010.

Note: Study C02-009 was a 28-week trial that included placebo and febuxostat 240 mg QD treatment groups. Thus, changes to Week 52 for these 2 groups of subjects were not relevant and no data are displayed.

a Statistically significant difference versus allopurinol 300/100 mg QD (p<0.05) using ANOVA.

m Statistically significant difference versus febuxostat 120 mg QD (p<0.05) using ANOVA.

Cross-reference: Statistical Table 4.1.2.3

Continuous Exposure in Phase 2/3 Studies

Among subjects with continuous exposure in the Phase 2/3 studies, small mean changes from baseline to each visit were identified for various endocrinology parameters that were similar across treatment groups.

Urinalysis

Laboratory analyses over time for urinalysis were done only for the continuous variables pH and specific gravity.

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Phase 3 Controlled Studies

Statistically significant differences were observed between the febuxostat 120 mg QD and both the febuxostat 80 mg QD and allopurinol 300/100 mg QD treatment groups for the mean change from baseline to the Week 28 Visit in **specific gravity** (Table 29).

Sporadic statistically significant treatment group differences were observed at various other timepoints for specific gravity and pH. Statistically significant changes from baseline were found for **pH and specific gravity**; these mean changes from baseline were small.

There was no new information submitted with safety update.

Table 29 (Sponsor's Table 4.1d, ISS)

Statistically Significant Treatment Group Differences in Mean Change from Baseline to the Week 28 and/or Week 52 Visits - Urinalysis Parameters (Phase 3 Controlled Studies)

Urinalysis Parameter	Placebo			Febuxostat 80 mg QD			Febuxostat 120 mg QD			Febuxostat 240 mg QD			Allopurinol 300/100 mg QD		
	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)
Specific Gravity															
Baseline	122	1.0186	0.00602	490	1.0192	0.00584	489	1.0189	0.00634	121	1.0181	0.00575	492	1.0194	0.00585
Mean Δ at Week 28	96	0.0007	0.00614	346	0.0009 ^a	0.00606	343	0.0012 ^a	0.00588	80	0.0004	0.00601	405	-0.0001	0.00636

Phase 3 studies included: C02-009 and C02-030.

a Statistically significant difference versus allopurinol 300/100 mg QD ($p \leq 0.05$) using ANOVA.

m Statistically significant difference versus febuxostat 120 mg QD ($p \leq 0.05$) using ANCOVA.

Cross-reference: Statistical Table 4.1.2.4

Continuous Exposure in Phase 2/3 Studies

Among subjects with continuous exposure in the Phase 2/3 studies, small mean changes from baseline to each visit were identified for pH and specific gravity that were similar across treatment groups.

7.1.5.3.2 Analyses focused on outliers or shifts from normal to abnormal

In this section, the shifts in laboratory values from baseline to post-baseline visits relative to the reference range as specified by the central laboratory were summarized. For the Phase 3 controlled studies, pairwise comparisons of the percentage of subjects with shifts in values were made between the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups. For shifts to high post-baseline values, only subjects with normal or low values at baseline were included. For shifts to low post-baseline values, only subjects with normal or high values at baseline were included.

The sponsor identified thresholds for each laboratory parameter for safety signal detection. Values outside of these thresholds that worsened from baseline were determined to have an increased possibility of representing a medically significant event if caused by therapy and are potentially concerning. However, such values may also represent population variation or be within the expected range for the type of subjects enrolled. Potentially concerning laboratory values were reviewed in the context of the individual subject and as a group to determine whether they were actually of concern and whether they represented a pattern of adverse drug reaction.

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Additionally, elevations in liver function test values were summarized by study type or treatment group based on pre-specified criteria.

Hematology
Phase 3 Controlled Studies

A statistically significant difference was observed between the febuxostat 80 mg QD and allopurinol 300/100 mg QD treatment groups for the shift from baseline to high at post-baseline in **neutrophils** and between the febuxostat 120 mg QD and allopurinol 300/100 mg QD treatment groups for the shift from baseline to high at post-baseline in **MCV** (Table 30). A statistically significant difference was observed between the febuxostat 120 mg QD and allopurinol 300/100 mg QD treatment groups for the shift from normal or high at baseline to low at post-baseline in **MCH**. However, no clinically meaningful trends were observed. No statistically significant differences were observed between the febuxostat 80 mg QD and febuxostat 120 mg QD treatment groups for the shift to high or low in any hematology parameter.

Table 30 (Sponsor's Table 4.2a, ISS)
Statistically Significant Treatment Group Differences in Shifts to High or Low Hematology Parameters (Phase 3 Controlled Studies)

Hematology Parameter	Placebo n/N (%)	Febuxostat 80 mg QD n/N (%)	Febuxostat 120 mg QD n/N (%)	Febuxostat 240 mg QD n/N (%)	Allopurinol 300/100 mg QD n/N (%)
MCV					
Shift to High	9/122 (7%)	62/491 (13%)	46/391 (9%) ^a	10/121 (8%)	74/493 (15%)
MCH					
Shift to Low	1/122 (<1%)	2/491 (<1%)	1/491 (<1%) ^a	2/121 (2%)	8/493 (2%)
Neutrophils					
Shift to High	22/122 (18%)	71/491 (14%) ^a	83/391 (17%)	18/121 (15%)	103/493 (20%)

Phase 3 studies included: C02-009 and C02-010.

^a Statistically significant difference versus allopurinol 300/100 mg QD (p<0.05) using Fisher's exact test.

Cross-reference: Statistical Table 4.2.1

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A statistically significant difference was observed between the febuxostat 80 mg QD and allopurinol 300/100 mg QD treatment groups for the proportion of subjects with potentially concerning high **WBC** values (3% and 1%, respectively); however, this effect was not seen at higher febuxostat doses. A statistically significant difference was also observed between the febuxostat 120 mg QD and allopurinol 300/100 mg QD treatment groups for the proportion of subjects with potentially concerning high **PTT** values (2% and <1%, respectively). No other statistically significant differences were observed between the treatment groups for the proportion of subjects with any specific potentially concerning hematology parameter (Table 31).

Table 31 (Sponsor's Table 4.2b, ISS)
Proportions of Subjects with Potentially Concerning Hematology Values (Phase 3 Controlled Studies)

Parameter (units) Criteria	Potentially Concerning Criterion	Treatment Group n (%)				
		Placebo (N=122)	Febuxostat 80 mg QD (N=491)	Febuxostat 120 mg QD (N=491)	Febuxostat 240 mg QD (N=121)	Allopurinol 300/100 mg QD (N=493)
Hemoglobin (g/dL) Low	F: ≤ 9.5 or ≥ 2.8 ↓ from BL M: ≤ 11.5 or ≥ 2.8 ↓ from BL	4 (3%)	31 (6%)	18 (4%)	3 (2%)	28 (6%)
MCV (fL) Low High	$\leq 0.8 \times$ LLN $\geq 1.2 \times$ ULN	0 0	2 (<1%) 1 (<1%)	0 0	0 0	0 0
MCH (pg) Low	$\leq 0.8 \times$ LLN	0	2 (<1%)	1 (<1%)	0	0
Reticulocytes (%) High	$\geq 1.5 \times$ ULN	1 (<1%)	0	2 (<1%)	1 (<1%)	0
Platelet Count ($\times 10^3$ /mL) Low High	≥ 700	0 0	0 1 (<1%)	0 1 (<1%)	0 0	2 (<1%) 0
Nucleated RBC (%) High	≥ 1	0	2 (<1%)	0	0	1 (<1%)
WBC Count ($\times 10^3$ /mL) Low High	≤ 2.8 ≥ 15.0	1 (<1%) 5 (4%)	1 (<1%) 17 (3%) ^a	3 (<1%) 12 (2%)	0 2 (2%)	2 (<1%) 7 (1%)
Neutrophil Count ($\times 10^3$ /mL) Low High	≤ 1.4 ≥ 15.0	0 0	7 (1%) 4 (<1%)	6 (1%) 1 (<1%)	1 (<1%) 0	8 (2%) 1 (<1%)
Lymphocyte Count ($\times 10^3$ /mL) Low	≤ 0.4	0	2 (<1%)	0	1 (<1%)	1 (<1%)
Eosinophil Count ($\times 10^3$ /mL) High	≥ 0.6	4 (3%)	26 (5%)	20 (4%)	6 (5%)	24 (5%)
Basophil Count ($\times 10^3$ /mL) High	≥ 0.6	0	1 (<1%)	0	0	0
Myelocytes ($\times 10^3$ /mL) High	If any	0	1 (<1%)	0	1 (<1%)	0
Promyelocytes ($\times 10^3$ /mL) High	If any	0	1 (<1%)	0	0	0
Metamyelocytes ($\times 10^3$ /mL) High	If any	1 (<1%)	1 (<1%)	1 (<1%)	0	0
Blasts ($\times 10^3$ /mL) High	If any	0	1 (<1%)	0	0	0
PT (seconds) High	$\geq 1.2 \times$ ULN	(N=116) 3 (3%)	(N=441) 10 (2%) ^a	(N=447) 10 (2%)	(N=106) 1 (<1%)	(N=461) 5 (1%)
PTT (seconds) High	$\geq 1.2 \times$ ULN	(N=116) 2 (2%)	(N=440) 5 (1%)	(N=447) 10 (2%) ^a	(N=105) 1 (<1%)	(N=461) 2 (<1%)

Phase 3 studies included: C02-009 and C02-030.

F = female; BL = baseline; M = male; LLN = lower limit of normal; ULN = upper limit of normal

Note: Treatment group sample sizes represent the numbers of subjects with data. Potentially concerning value was also more extreme than subject's baseline value.

^a Statistically significant difference versus allopurinol 300/100 mg QD ($p < 0.05$) using Fisher's exact test.

Only parameters with at least 1 subject with a potentially concerning value are included in this table.

Cross-reference: Statistical Table 4.4.2

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Reviewer's comments:

- Most of the findings in the table do not seem to present a serious concern. Despite statistically significant difference between active treatment groups for high WBC parameter there is no difference between the treatment groups and placebo, and numerically placebo group looks even worse (4%) than all of the treatment groups (3%, 2%, and 1%)
- Noticeable shift to high PTT values in febuxostat groups, especially in 120 mg group when compared to allopurinol group may provide a clue to why there were several patients on coumadin whose INR value increased significantly while on co-administered febuxostat.

Continuous Exposure in Phase 2/3 Studies

In subjects with continuous exposure in the Phase 2/3 studies, the proportion of febuxostat subjects with shifts to high or low was similar across treatment groups. The most frequently occurring shifts to high were **neutrophils (15%), WBC (14%), and MCV (10%)**. Additionally, the most frequently occurring shift to low was **PTT (17%)**.

Chemistry

Phase 3 Controlled Studies

The proportion of subjects with a shift to high at post-baseline in ALT was similar across all treatment groups (29%-34%). A shift to high was noted for **BUN**, which was highest in the febuxostat 240 mg QD group (24%) compared to placebo (13%) and also higher compared to the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD groups (19%, 19% and 17%, respectively). Additionally, statistically significant differences were observed between the febuxostat 80 mg QD and febuxostat 120 mg QD treatment groups for the shift from baseline to high at post-baseline in **creatinine (8% and 12%, respectively)** and **triglycerides (33% and 27%, respectively)**.

Table 32 (Sponsor's Table 4.2c, ISS)
Statistically Significant Treatment Group Differences in Shifts to High or Low – Chemistry Parameters (Phase 3 Controlled Studies)

Chemistry Parameter	Placebo		Febuxostat 80 mg QD		Febuxostat 120 mg QD		Febuxostat 240 mg QD		Allopurinol 300/100 mg QD	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
Creatinine										
Shift to High	17/129	(13%)	42/508	(8%) ^m	62/506	(12%) ^a	15/127	(12%)	54/506	(11%)
Triglyceride										
Shift to High	36/129	(28%)	170/508	(33%) ^m	135/506	(27%) ^a	39/127	(31%)	169/506	(33%)

Phase 3 studies included: C02-009 and C02-010.

^a Statistically significant difference versus allopurinol 300/100 mg QD (p<0.05) using Fisher's exact test.

^m Statistically significant difference versus febuxostat 120 mg QD (p<0.05) using Fisher's exact test.

Cross-reference: Statistical Table 4.2.2

No statistically significant differences were observed between the treatment groups for the proportion of subjects with any specific potentially concerning chemistry parameter. However, the proportion of subjects with a potentially concerning ALT elevation was **numerically higher in the febuxostat 80 mg QD and febuxostat 120 mg QD treatment groups (13% each) compared to the allopurinol 300/100 mg QD treatment group (10%)**.

In addition, the proportion of subjects with a potentially concerning **BUN elevation** was numerically higher in the febuxostat 240 mg QD treatment group (16%), as well as the febuxostat 120 mg QD group (9%) compared to the other treatment groups (6-7%; **Table 33**).

However, when only subjects who were not taking NSAIDs/COX-2 inhibitors at the time of the laboratory assessment were analyzed, the incidence of potentially concerning high BUN was similar in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD

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treatment groups, as well as in the placebo group. These results indicate that the increase in BUN were due to the increased use of NSAIDs/COX-2 inhibitors in the active treatment groups following treatment with a urate-lowering drug. However, it was still higher in the febuxostat 240 mg QD group. It should be noted that this change in BUN was not accompanied by a shift to high for creatinine or by a mean decrease from baseline for measured Cl_{cr}.

Table 33 (Sponsor's Table 4.2d, ISS)
Proportions of Subjects with Potentially Concerning Chemistry Values
(Phase 3 Controlled Studies)

Parameter (units) Criteria	Potentially Concerning Criterion	Treatment Group n (%)				
		Placebo (N=129)	Febuxostat 80 mg QD (N=508)	Febuxostat 120 mg QD (N=506)	Febuxostat 240 mg QD (N=127)	Allopurinol 300/100 mg QD (N=506)
Sodium (mEq/L)						
Low	≤124	0	1 (<1%)	0	0	0
High	≥151	1 (<1%)	5 (<1%)	3 (<1%)	0	3 (<1%)
Potassium (mEq/L)						
Low	≤2.9	1 (<1%)	0	1 (<1%)	0	1 (<1%)
High	≥3.9	4 (3%)	4 (<1%)	4 (<1%)	3 (2%)	2 (<1%)
Chloride (mEq/L)						
Low	≤79	0	1 (<1%)	0	0	0
High	≥121	0	1 (<1%)	0	0	0
Bicarbonate (mEq/L)						
Low	≤17	2 (2%)	0 (2%)	11 (2%)	0	8 (2%)
Glucose (mg/dL)						
Low	≤49	0	5 (<1%)	2 (<1%)	0	1 (<1%)
High	≥301	3 (2%)	6 (1%)	7 (1%)	1 (<1%)	1 (<1%)
BUN (mg/dL)						
High	≥31	8 (6%)	38 (7%)	44 (9%)	20 (16%)	33 (7%)
Creatinine (mg/dL)						
High	≥1.5 & ≥0.3 ↑ from BL	8 (6%)	23 (5%)	27 (5%)	12 (9%)	29 (6%)
Calcium (mg/dL)						
High	≥12.0	0	1 (<1%)	1 (<1%)	0	0
Inorganic Phosphorus (mg/dL)						
Low	≤1.5	0	0	1 (<1%)	2 (2%)	1 (<1%)
Total Bilirubin (mg/dL)						
High	≥2.0	1 (<1%)	4 (<1%)	10 (2%)	4 (3%)	3 (<1%)
Alkaline Phosphatase (U/L)						
High	≥2 x ULN	0	4 (<1%)	1 (<1%)	0	0
AST (U/L)						
High	≥2 x ULN	7 (5%)	35 (7%)	38 (8%)	11 (9%)	34 (7%)
ALT (U/L)						
High	≥2 x ULN	8 (6%)	65 (13%)	65 (13%)	19 (15%)	49 (10%)
LDH (U/L)						
High	≥2 x ULN	0	1 (<1%)	1 (<1%)	0	1 (<1%)
Total Cholesterol (mg/dL)						
High	≥350 & ≥100 ↑ from BL	0	2 (<1%)	1 (<1%)	0	4 (<1%)
Triglyceride (mg/dL)						
High	≥2 x ULN & ≥100 ↑ from BL	17 (13%)	73 (14%)	82 (16%)	17 (13%)	85 (17%)

Phase 3 studies included: C02-609 and C02-610.

BL = baseline; ULN = upper limit of normal

Only parameters with at least 1 subject with a potentially concerning value are included in this table.

Note: Treatment group sample sizes represent the numbers of subjects with data. Potentially concerning value was also more extreme than subject's baseline value.

Cross-reference: Statistical Table 4.4.2

Reviewer's comments:

- There are higher rates of increased total bilirubin values in febuxostat 120 and 240 mg groups (10/506 and 4/127, respectively) compared to febuxostat 80 mg and allopurinol groups (4/508 and 5/506, respectively). Similar finding is observed with AST values (38/506 and 11/127 vs. 35/508 and 34/506).

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- *Febuxostat 80 mg and 120 mg groups have the highest rates of increased ALT (65/508, or 13% and 65/506, or 13% respectively) compared to allopurinol and placebo groups (49/506, or 10% and 8/129, or 6%, respectively).*
- *This might present a signal for potential hepatotoxicity.*

Continuous Exposure in Phase 2/3 Studies

The proportion of subjects with shifts to low or high was comparable between the febuxostat 40-240 mg QD and allopurinol 300/100 mg QD treatment groups. In febuxostat 40-240 mg QD subjects with continuous exposure in the Phase 2/3 studies, the most frequently occurring shifts to high were **glucose (36%), AST (34%), ALT (32%), creatine phosphokinase (CPK) and triglyceride (30% each), BUN (21%), gamma glutamyl transferase (GGT) and sodium (17% each), chloride (13%), calcium, amylase, and creatinine (12% each), measured Cl_{cr} (11%), and albumin and total cholesterol (10% each)**. Additionally, the most frequently occurring shifts to low were total cholesterol (22%) and measured Cl_{cr} (17%).

In allopurinol 300/100 mg QD subjects with continuous exposure in the Phase 2/3 studies, the most frequently occurring shifts to high were **glucose (40%), triglyceride (33%), AST and ALT (32% each), BUN (17%), measured Cl_{cr} (14%), amylase (13%), albumin and sodium (11% each), and creatinine (10%)**. Additionally, the most frequently occurring shifts to low were total cholesterol (26%) and measured Cl_{cr} (18%).

The proportion of subjects with potentially concerning chemistry parameters was low and similar across treatment groups for most parameters. Of note, potentially concerning high **triglyceride, ALT, and CPK** values were experienced by 17%, 14%, and 11% of febuxostat 40-240 mg QD subjects, respectively. Potentially concerning high triglyceride and ALT values were experienced by 17% and 10% of allopurinol 300/100 mg QD subjects. **Creatine phosphokinase was not included in the laboratory evaluation in the Phase 3 studies (C02-009, C02-010, and C02-021).**

Endocrinology

Phase 3 Controlled Studies

A statistically significant difference was observed between the febuxostat 80 mg QD and febuxostat 120 mg QD treatment groups for the shift from baseline to high at post-baseline (no subjects and 1%, respectively) in **total T₃**.

However, no clinically meaningful trends were observed.

No statistically significant differences were observed between the treatment groups for the proportion of subjects with any specific potentially concerning endocrinology parameter (**Table 34**).

Table 34 (Sponsor's Table 4.2e, ISS)
Proportions of Subjects with Potentially Concerning Endocrinology Values
(Phase 3 Controlled Studies)

Parameter (units) Criteria	Potentially Concerning Criterion	Treatment Group n (%)				
		Placebo (N=134)	Febuxostat 80 mg QD (N=523)	Febuxostat 120 mg QD (N=520)	Febuxostat 240 mg QD (N=134)	Allopurinol 300/100 mg QD (N=521)
TSH (mIU/mL)	Low ≤ 0.1	0	1 (<1%)	0	2 (2%)	1 (<1%)
	High ≥ 5.5	0	8 (2%)	10 (3%)	1 (1%)	12 (3%)
Total T ₄ (mcg/dL)	Low $\leq 0.8 \times \text{LLN}$	0	2 (<1%)	1 (<1%)	0	2 (<1%)
	High ≥ 13.0	0	1 (<1%)	1 (<1%)	0	0
Total T ₃ (ng/dL)	Low $\leq 0.8 \times \text{LLN}$	0	0	1 (<1%)	0	0
	Low	0	0	0	0	2 (<1%)

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LLN = lower limit of normal

Phase 3 studies included: C02-009 and C02-010.

Only parameters with at least 1 subject with a potentially concerning value are included in this table.

Note: Treatment group sample sizes represent the numbers of subjects with data. Potentially concerning value was also more extreme than subject's baseline value.

Cross-reference: Statistical Table 4.4.2

Continuous Exposure in Phase 2/3 Studies

In subjects with continuous exposure in the Phase 2/3 studies, the proportion of febuxostat subjects with shifts to high or low was low (83%) for all endocrinology parameters. Similar results were observed in the allopurinol 300/100 mg QD treatment group.

Urinalysis

Shift analysis was done only for pH and specific gravity. An analysis of potentially concerning results was done for all character urinalysis values.

Phase 3 Controlled Studies

A statistically significant difference was observed between the febuxostat 120 mg QD and allopurinol 300/100 mg QD treatment groups for the shift from baseline to high at post-baseline (8% and 5%, respectively) in **urine specific gravity**.

However, no clinically meaningful trends were observed.

No consistent trend across doses or treatment groups in the proportion of subjects with potentially concerning urinalysis values was identified, although a statistically significant difference was observed between the febuxostat 80 mg QD and febuxostat 120 mg QD treatment groups for the proportion of subjects with potentially concerning urine glucose values (1% and 3%, respectively; **Table 35**). However, this treatment difference was not considered clinically significant.

Table 35 (Sponsor's Table 4.2f, ISS)
Proportions of Subjects with Potentially Concerning Urinalysis Values
(Phase 3 Controlled Studies)

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Parameter (units) Criteria	Potentially Concerning Criterion	Treatment Group n (%)				
		Placebo (N=122)	Febuxostat 80 mg QD (N=490)	Febuxostat 120 mg QD (N=489)	Febuxostat 240 mg QD (N=121)	Allopurinol 300/100 mg QD (N=493)
pH High	≥8.5	0	0	1 (<1%)	0	1 (<1%)
Specific Gravity High	≥1.040	2 (2%)	4 (<1%)	3 (<1%)	1 (<1%)	2 (<1%)
Protein (+) High	≥2+ or ≥100 mg/dL	6 (5%)	21 (4%)	20 (4%)	7 (6%)	26 (5%)
Glucose (+) High	≥2+ or ≥500 mg/dL	4 (3%)	6 (1%) ^m	16 (3%)	1 (<1%)	12 (2%)
Ketones (+) High	≥2+ or ≥40 mg/dL	2 (2%)	9 (2%)	4 (<1%)	0	4 (<1%)
Blood (+) High	≥2+	2 (2%)	4 (<1%)	6 (1%)	2 (2%)	4 (<1%)
RBC (#/hpf) High	≥10 RBC/hpf	3 (2%)	24 (5%)	19 (4%)	5 (4%)	23 (5%)
WBC (#/hpf) High	≥20 WBC/hpf	5 (4%)	15 (3%)	18 (4%)	6 (5%)	22 (4%)

Phase 3 studies included: C02-009 and C02-010.

hpf = high power field

Only parameters with at least 1 subject with a potentially concerning value are included in this table.

Note: Treatment group sample sizes represent the numbers of subjects with data. Potentially concerning value was also more extreme than subject's baseline value.

m Statistically significant difference versus febuxostat 120 mg QD (p<0.05) using Fisher's exact test.

Cross-reference: Statistical Tables 4.4.2 and 4.3.2

Continuous Exposure in Phase 2/3 Studies

In subjects with continuous exposure in the Phase 2/3 studies, the proportion of febuxostat subjects with shifts to high was low for pH and specific gravity. The most frequently occurring shift to low was specific gravity.

7.1.5.3.3 Marked outliers and dropouts for laboratory abnormalities

See also 7.1.6.3.2 for analyses of potentially concerning laboratory values.

In addition, there were a few patients who discontinued the study drug due to changes in laboratory parameters. One patient in febuxostat 120 mg arm discontinued due to anemia, one on allopurinol and two in febuxostat 120 mg due to thrombocytopenia and two in febuxostat 80 mg due to increased triglycerides.

7.1.5.4 Special assessments

Hepatic Effects: Adverse Events (Phase 1 Studies)

In the Phase 1 studies, 1 subject each experienced hepatitis (Subject 622 in Study C02-006), aspartate aminotransferase increase (Subject 612 in Study C02-006), and transaminases increased (Subject 108 in Study C02-013) which led to premature discontinuation of study drug. Each of the events was considered to be related to study drug by the investigators. It should be

noted that Subjects 612 and 622 received colchicine and Subject 108 received naproxen concomitantly.

Reviewer comments:

- *Subject 622 was on Febuxostat 120 mg and colchicine and presented with increased ALT/AST. No bilirubin values were provided. No hepatitis serologies were performed.*
- *Subject 612 was on Febuxostat 120 mg and colchicine and presented with increased moderate AST elevation (>3 ULN) and severe CPK elevation (>40 ULN)*
- *Subject 108 was on Febuxostat 80 mg and naproxen and presented with mildly elevated transaminases*

Hepatic Effects: Laboratory Results

In addition to the adverse event assessment, the effect of febuxostat on hepatic disorders was assessed by laboratory analyses, including ALT, AST, alkaline phosphatase, and total bilirubin. In this section, the laboratory analysis focuses on elevations of 2 x upper limit of normal (ULN), 3 x ULN, 5 x ULN, and 10 x ULN for ALT and AST. In addition, concurrent elevations of ALT/AST with alkaline phosphatase 2 x ULN, concurrent elevations of ALT/AST with total bilirubin ≥ 2 mg/dL, and concurrent elevations of ALT and AST are presented, as well as shifts from baseline to post-baseline visits relative to the reference range.

Subjects 4894, 2321, and 2439 were presented in **10x Upper Limit of Normal**

Reviewer's comments:

- *Subject 4894 was on febuxostat 240 mg at the time of event and in addition to increased transaminases, had increased bilirubin (10.3). The hepatitis panel was negative. An ultrasound of the liver revealed cholelithiasis and question of fatty infiltration of the liver.*
- *Subject 2321 was on allopurinol 300 mg and colchicine.*
- *Subject 2439 was on febuxostat 80 mg and colchicine at the time of event. Had elevated bilirubin as well. Was diagnosed with an acute Hepatitis C.*
- *In addition, one subject in phase 1 study (709) while on febuxostat 70 mg presented with elevated liver tests >10 ULN. Bilirubin values are not provided.*
- *Another 7 subjects in febuxostat groups and 4 subjects in allopurinol group had ALT >5 ULN with normal bilirubin values*

Subjects 4009, 4181, and 1018 were presented in **2x Upper Limit of Normal Concurrent** with a Total Bilirubin Value ≥ 2.0 mg/dL

Reviewer's comments:

- *Subject 4009 was on allopurinol 300 mg and naproxen at the time of event. Diagnosed with cholelithiasis. Highest bilirubin values was 5.3*
- *Subject 4181 was on febuxostat 80 mg at the time of event. Highest total bili was 2.0*
- *Subject 1018 was on febuxostat 80 mg and colchicine at the time of event. Highest bilirubin value was 7.4*
- *The numbers of adverse events of elevated LFTs are small, there is no apparent difference between groups and there is no obvious dose-proportional effect. It appears that both drugs, febuxostat and allopurinol, pose a risk for potential hepatotoxicity. Addition of an NSAID or colchicine might aggravate such a risk. Therefore the monitoring of LFTs should be recommended in the label.*

7.1.6 Vital Signs

7.1.6.1 Overview of vital signs testing in the development program

Vital signs (including temperature, blood pressure, heart rate, respiratory rate, all counted for 30 seconds after 3 minutes in the sitting position) and weight were taken at protocol-specified timepoints. The subject's height was recorded at the Screening Visit. Significant adverse changes in vital signs occurring after the subject signed the informed consent form for the study were to be recorded as adverse events.

During the PK/PD Substudy Visits in Study C02-009, vital signs (including temperature, blood pressure, heart rate and respiratory rate, all counted for 30 seconds after 3 minutes in the sitting position) were taken for both the 0.75-2.0 hour postdose blood collection and the 2.5-4.0 hour postdose blood collection.

7.1.6.2 Standard analyses and explorations of vital signs data

7.1.6.2.1 Analyses focused on measures of central tendencies

Phase 3 Controlled Studies

In the Phase 3 controlled studies, a statistically significant difference was observed between the febuxostat 80 mg QD and febuxostat 120 mg QD treatment groups for the **mean change from baseline to the Week 28 Visit in diastolic blood pressure.**

Reviewer's comments:

- *Statistical Table 5.1.2 presents other sporadic statistically significant treatment group differences for systolic blood pressure, diastolic blood pressure, and pulse at various timepoints. Each of the mean changes from baseline was small and not considered clinically significant.*

7.1.6.2.2 Analyses focused on outliers or shifts from normal to abnormal

Table 36 (Sponsor's Table 5.1a, ISS) Criteria for Potentially Concerning Vital Sign Values

Variable (Units)	Low Threshold [#]	High Threshold [#]
Systolic Blood Pressure (mm Hg)	<85 or drop >30 from baseline	180
Diastolic Blood Pressure (mm Hg)	<45 or drop >20 from baseline	110
Pulse (Beats/min)	<50	120

Two or more readings meeting either the low or high threshold and more extreme than the subject's baseline value. Baseline was defined as the last measurement prior to the first dose of study drug.

Cross-reference: Statistical Table 5.2

**Table 37 (Sponsor's Table 5.3.2)
Number and Percentage of Subjects with Potentially Concerning Vital Sign Values in Phase 3 Controlled Studies**

Variable/ Criteria	Placebo (N=134)	Febuxostat 80 mg (N=523)	Febuxostat 120 mg (N=526)	Febuxostat 240 mg (N=134)	Allopurinol 200/300 mg (N=521)
Systolic Blood Pressure (mm Hg)					
Low	2/ 123 (2%)	22/ 493 (4%)	19/ 496 (4%)	5/ 122 (4%)	22/ 493 (4%)
High	1/ 123 (<1%)	3/ 494 (<1%)	3/ 496 (<1%)	1/ 122 (<1%)	3/ 493 (<1%)
Diastolic Blood Pressure (mm Hg)					
Low	5/ 123 (4%)	17/ 494 (3%)	12/ 496 (2%)	6/ 122 (5%)	17/ 493 (3%)
High	1/ 123 (<1%)	1/ 494 (<1%)	0/ 496	1/ 122 (<1%)	6/ 493 (1%)
Pulse (Beats/min)					
Low	2/ 123 (2%)	4/ 494 (<1%)	3/ 496 (<1%)	0/ 122	2/ 493 (<1%)
High	0/ 123	0/ 494	0/ 496	0/ 122	0/ 493

Studies included: C02-006 and C02-018.
Criteria for potentially concerning vital sign values are presented in Table 5.2.

Reviewer's comments:

- Numerically, there were more patients in Allopurinol group with increased potentially concerning diastolic blood pressure values (6/493) compared to febuxostat 80 mg (1/494) and febuxostat 120 mg (0/496)

**Table 38 (Sponsor's Table 5.3.3)
Number and Percentage of Subjects with Potentially Concerning Vital Sign Values for Subjects with Continuous Exposure in Phase 2/3 Studies**

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Variable/ Criteria	Febuxostat 40 - 240 mg (N=1322)	Allopurinol 300/100 mg (N=532)
Systolic Blood Pressure (mm Hg)		
Low	52/1322 (4%)	22/ 504 (4%)
High	11/1322 (<1%)	3/ 504 (<1%)
Diastolic Blood Pressure (mm Hg)		
Low	45/1322 (3%)	18/ 504 (4%)
High	4/1322 (<1%)	5/ 504 (1%)
Pulse (Beats/min)		
Low	19/1322 (1%)	2/ 504 (<1%)
High	6/1322	3/ 504

Subjects included: TMX-99-004, TMX-01-005, C02-005, C01-010, and C01-021. Continuous exposure summarized data from subjects who received the same treatment (regardless of dose) in an extension study as in the previous study. For details see the statistics methods section of the ISE. Febuxostat doses include: 40 mg, 80 mg, 120 mg, and 240 mg. Criteria for potentially concerning vital sign values are presented in Table 5.2.

7.1.6.2.3 Marked outliers and dropouts for vital sign abnormalities

One patient in Febuxostat 80 mg discontinued from the trial due to increased BP, and one due to decreased BP. One patient in Allopurinol group discontinued from the trial due to bradycardia

Reviewer's comments:

- Febuxostat 80 mg QD, febuxostat 120 mg QD and febuxostat 240 mg QD appears to have no or little effect on vital signs

7.1.6.3 Additional analyses and explorations

None

7.1.7 Electrocardiograms (ECGs)

7.1.7.1 Overview of ECG testing in the development program, including brief review of preclinical results

Standard 12-lead resting electrocardiograms (ECGs) were performed at protocol-specified timepoints in all Phase 2 and 3 studies, in Phase 1 Study C02-023 Part B, and other Phase 1 studies. The investigator assessed the ECG tracing and indicated clinical significance. Clinically significant changes in ECGs occurring after the subject signed the informed consent form for the study were to be recorded as adverse events.

The effect of febuxostat on cardiac repolarization was assessed in healthy volunteers in a definitive QT interval study (C02-023 Part B), in 4 Phase 1 studies (TMX-99-001, TMX-00-002, TMX-00-003, and TMX-00-006) and in subjects with hyperuricemia associated with gout in a substudy of Study C02-009.

In Study C02-023 Part B, resting 12-lead ECGs were obtained during screening. On Day -1 (the day before dosing), ECGs were obtained at 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, 180, 195, 210, 240, 360, and 480 minutes and at 12 hours prior to dosing.

On Day 1, ECGs were obtained 30 minutes prior to dosing, and at 30, 60, 90, 120, 150, 180, and 240 minutes postdose. On Days 2 and 3, ECGs were obtained 1 hour postdose.

On Day 4, ECGs were obtained 30 minutes prior to dosing and at 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, 180, 195, 210, 240, 360, and 480 minutes and at 12 and 24 hours postdose. For each ECG, the following parameters were measured: PR interval, QRS duration, RR interval, QT interval, Fridericia corrected QT interval (QT_{cF}), Bazett corrected QT interval (QT_{cB}), and ST segment. In addition, T and U wave morphology was recorded. b(4)

ECG machines (model _____) were used to obtain the ECG tracings. After investigator review, ECGs were transmitted digitally to _____. All ECG reviews occurred while blinded and were confirmed by a central cardiologist. To minimize within-subject differences due to variations in cardiologist readings, the same cardiologist (blinded to treatments) read all ECGs obtained during the study.

In Study C02-009, subjects enrolled at sites that participated in the PK/PD substudy each had a total of 6 ECGs performed using standardized equipment provided by _____. b(4)

- Day -2 Visit: 3 ECGs performed 15 minutes apart
- PK/PD Substudy Visit (between the Week 16 and Week 28 Visits): 1 ECG performed within 15 minutes of the 0.75-2.0 hours postdose blood collection and not less than 0.75 hours postdose
- PK/PD Substudy Visit (between the Week 16 and Week 28 Visits): 1 ECG within 15 minutes of the 2.5-4.0 hours postdose blood collection and not more than 4.0 hours postdose
- Week 28 Visit (or upon premature discontinuation): 1 ECG

Paper copies of the ECG tracings were printed and reviewed at the site. In addition, these ECG data were transmitted digitally to _____ in accordance with instructions provided separately to the site. Each substudy site was provided with instructions and training on the use of the ECG machines. All ECG reviews occurred while blinded and were confirmed by a central cardiologist. To minimize within-subject differences due to variations in cardiologist readings, the same cardiologist (blinded to treatments) read all ECGs obtained during the study. b(4)

In the 4 Phase 1 studies (TMX-99-001, TMX-00-002, TMX-00-003, and TMX-00-006), ECG tracings were obtained by equipment provided by the site and were evaluated by the site investigator.

7.1.7.2 Standard analyses and explorations of ECG data

7.1.7.2.1 Analyses focused on outliers or shifts from normal to abnormal

Eighteen subjects (1 placebo, 5 febuxostat 80 mg QD, 6 febuxostat 120 mg QD, and 6 allopurinol 300/100 mg QD) experienced a change from baseline that was considered clinically significant by the investigator (Table 39). There were no specific patterns in ECGs changes and no dose response noted.

Table 39 (Sponsor's Table 5.3a) Summary of Clinically Significant Changes from Baseline in Electrocardiogram Results (Phase 2/3 Studies)

Study/Subject/ Age/Gender	Investigator Comment(s)	Study Day ^a
Placebo		
C02-009/ 4910/52/Male	Sinus tachycardia; possible left atrial enlargement, possible left ventricular hypertrophy	197 (1)
Febuxostat 80 mg QD		
TMX-01-005/ 1699/66/Male	Improved T-wave inversion and ST-T changes	29 (1)
TMX-01-005/ 1692/52/Male	Atrial fibrillation with rapid ventricular response	842 (cumulative day 870 from Study TMX-00-004)
C02-010/ 2685/72/Female	Left bundle branch block; old septal MI	169 (113)
C02-010/ 2695/58/Male	Atrial fibrillation	372 (1)
C02-010/ 2824/44/Male	ST-T changes in chest leads 3/4/5 have occurred since 7/7/03	361 (1)
Febuxostat 120 mg QD		
TMX-01-005/ 1641/56/Male	Sinus tachycardia secondary to mild hypertension, tachycardia, otherwise normal	26 (cumulative day 58 from Study TMX-00-004)
C02-010/ 2865/52/Male	Pacemaker	371 (1)
C02-010/ 2615/72/Male	Premature ventricular contractions - Bradycardia	120 (6)
C02-009/ 4014/51/Male	Normal sinus rhythm; nonspecific ST-T changes infero-lateral leads; ischemia	207 (1)
C02-009/ 4308/68/Male	Atrial fibrillation	127 (21)
C02-009/ 4351/50/Male	Abnormal ECG	49 (2)
Allopurinol 300/100 mg QD		
C02-010/ 2305/61/Female	Supraventricular extrasystoles, intraventricular conduction defect, probably left ventricular hypertrophy	366 (1)
C02-010/ 2766/66/Male	Left ventricular hypertrophy with secondary repolarization abnormality	166 (106)
C02-010/ 2809/65/Male	Second degree heart block	363 (1)
C02-009/ 4688/55/Male	Normal sinus rhythm; left bundle branch block; abnormal ECG	200 (1)
C02-009/ 4458/62/Male	Atrial fibrillation	201 (2)
C02-009/ 4725/43/Male	T wave abnormality; possible inferior ischemia	196 (1)

MI = myocardial infarction

^a Number in parentheses represents the number of days relative to the last dose of study drug.

Cross-reference: Section 12.5.3 of TMX-00-004, TMX-01-005, C02-009, and C02-010 CSRs

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In the Phase 3 controlled studies, a similar proportion of subjects in the febuxostat 80 mg QD, febuxostat 120 mg QD, allopurinol 300/100 mg QD, febuxostat 240 mg QD, and placebo treatment groups had at least 1 ECG coded with MedDRA (10%, 11%, 11%, 13%, and 17%, respectively; Table 40).

The incidence of bradycardia was similar in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups (<1% each), as well as in the placebo and febuxostat 240 mg QD treatment groups (1% and <1%, respectively). The incidence of sinus arrhythmia was <1% in each of the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups and slightly higher in the placebo and febuxostat 240 mg QD treatment groups (4% and 3%, respectively);

Table 40 (Sponsor's Table 5.3b) Electrocardiogram Comments by Cardiologist Coded with MedDRA (Phase 3 Controlled Studies)

MedDRA High Level Term Preferred Terms	Treatment Group n (%)				
	Placebo (N=134)	Febuxostat 80 mg QD (N=523)	Febuxostat 120 mg QD (N=520)	Febuxostat 240 mg QD (N=134)	Allopurinol 300/100 mg QD (N=521)
Total Subjects with at Least 1 ECG Coded with MedDRA	23 (17%)	54 (10%)	59 (11%)	18 (13%)	57 (11%)
Cardiac Conduction Disorders Atrioventricular Block, Atrioventricular Block First Degree, Atrioventricular Block Second Degree, Bundle Branch Block, Bundle Branch Block Left, Bundle Branch Block Right, Conduction Disorder, Wolf-Parkinson-White Syndrome	3 (2%)	10 (2%)	8 (2%)	4 (3%)	14 (3%)
Ischaemic Coronary Artery Disorders Age Indeterminate Myocardial Infarction, Myocardial Infarction	0	1 (<1%)	2 (<1%)	0	2 (<1%)
Myocardial Disorders NEC Dilatation Atrial, Ventricular Hypertrophy	1 (<1%)	1 (<1%)	0	0	5 (<1%)
Rate & Rhythm Disorders NEC Bradycardia, Extrasystoles, Nodal Rhythm, Tachycardia	3 (2%)	5 (<1%)	6 (1%)	2 (1%)	5 (<1%)

NEC = not elsewhere classified

Phase 3 studies included: C02-G09 and C02-G10.

Cross-reference: Statistical Table 5.7

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MedDRA High Level Term Preferred Terms	Treatment Group n (%)				
	Placebo (N=134)	Febuxostat 80 mg QD (N=523)	Febuxostat 120 mg QD (N=520)	Febuxostat 240 mg QD (N=134)	Allopurinol 300/100 mg QD (N=521)
Supraventricular Arrhythmias Atrial Fibrillation, Atrial Flutter, Premature Atrial Contraction, Sinus Arrest, Sinus Arrhythmia, Sinus Bradycardia, Sinus Tachycardia, Supraventricular Extrasystoles	16 (12%)	21 (4%)	24 (5%)	8 (6%)	21 (4%)
Ventricular Arrhythmias & Cardiac Arrest Ventricular Extrasystoles	1 (<1%)	6 (1%)	10 (2%)	1 (<1%)	7 (1%)
ECG Investigations Electrocardiogram Abnormal, Electrocardiogram Normal, Electrocardiogram P Wave Abnormal, Electrocardiogram Pacemaker Spike, Electrocardiogram Poor R-Wave Progression, Electrocardiogram QRS Complex Abnormal, Electrocardiogram QRS Complex Prolonged, Electrocardiogram QT Prolonged, Electrocardiogram QT Shortened, Electrocardiogram Repolarisation Abnormality, Electrocardiogram ST Segment Abnormal, Electrocardiogram ST Segment Depression, Electrocardiogram ST Segment Elevation, Electrocardiogram ST-T Change, Electrocardiogram T Wave Abnormal, Electrocardiogram T Wave Amplitude Decreased, Electrocardiogram T Wave Inversion, QRS Axis Abnormal	4 (3%)	18 (3%)	18 (3%)	5 (4%)	17 (3%)
Cardiac Pacemaker Therapeutic Procedures Pacemaker Generated Rhythm, Electrocardiogram Pacemaker Spike	0	2 (<1%)	1 (<1%)	0	0

NEC = not elsewhere classified
Phase 3 studies included: C02-009 and C02-010.
Cross-reference: Statistical Table 5.7

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7.1.7.2.2 Marked outliers and dropouts for ECG abnormalities

For the majority of subjects in the Phase 1 studies, no clinically significant changes from baseline in ECG results were identified. Three subjects (1 febuxostat 10 mg BID, 1 febuxostat 40 mg QD, 1 febuxostat 80 mg QD) experienced a change from baseline that was considered clinically significant by the investigator (Table 41). One (Subject 1809) of these 3 subjects experienced a clinically significant improvement during treatment with febuxostat 10 mg BID.

Table 41 (Sponsor's Table 5.3c, ISS)
Summary of Clinically Significant Changes from Baseline in Electrocardiogram Results (Phase 1 Studies)

Study	Subject/Age/ Gender	Investigator Comment(s)	Study Day ^a
Febuxostat 10 mg BID (N=16)			
TMX-00-003	46/52/Female	Incomplete right bundle branch block developed on last ECG; clinically significant improvement	13 (1 hour postdose)
Febuxostat 40 mg QD (N=70)			
TMX-00-003	21/69/Male	Sinus bradycardia; peaked T-wave V4-V6; premature atrial contractions; irregular rhythm; clinically significant deterioration	1 (1 hour postdose)
Febuxostat 80 mg QD (N=49)			
TMX-99-001	1/60/54/Female	Frequent premature junctional contraction with aberrant conduction; clinically significant deterioration Normal; clinically significant improvement	3 15 (9)

^a Number in parentheses represents the number of days relative to the last dose of study drug.
Cross-reference: TMX-00-003 and TMX-99-001 CSRs

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7.1.7.3 Additional analyses and explorations

Analysis of QT Interval

The effect of febuxostat on cardiac repolarization as assessed by the QTc interval was formally investigated in Study C02-023 Part B. In addition, QT interval assessments were performed in 4 Phase 1 studies (TMX-99-001, TMX-00-002, TMX-00-003, and TMX-00-006) in healthy volunteers. Finally, the QT interval was assessed in a substudy of Phase 3 Study C02-009 in subjects with hyperuricemia associated with a history or presence of gout. QT interval results were corrected for heart rate using both the Fridericia formula (QT_{cF}) and the Bazett formula (QT_{cB}). In Study C02-023 Part B and in the substudy of Study C02-009, ECG tracings were obtained by standardized equipment provided by _____ ECG data were transmitted digitally to _____ s for evaluation by a central reader in a blinded fashion. All ECG results were confirmed by a central cardiologist. To minimize within-subject differences due to variations in cardiologist readings, the same cardiologist (blinded to treatments) read all ECGs obtained during the study. In Studies TMX-99-001, TMX-00-002, TMX-00-003, and TMX-00-006, ECG tracings were obtained by equipment provided by the site and were evaluated by the site investigator. Any clinically significant assessments were reported as adverse events on the appropriate CRFs.

b(4)

Study C02-023

Study C02-023 Part B was a Phase 1, double-blind, 4-period crossover trial that assessed the potential for a prolongation of the QT_c interval in healthy subjects after multiple doses of placebo, febuxostat 80 mg QD, febuxostat 300 mg QD, and moxifloxacin 400 mg QD (the active control). The study was designed so that each subject received all 4 dosing regimens. Each period consisted of 4 days of QD dosing. There was a 7-day washout interval between the last dose in a period and the first dose of the subsequent period.

On Day 1 of each period, subjects were dosed beginning at approximately 0845 in a staggered fashion, to facilitate logistics at the study site. Electrocardiograms were performed 30 minutes prior to dosing, and 30, 60, 90, 120, 150, 180, and 240 minutes after the administration of the study drug. On Days 2 and 3 of each period an ECG was obtained 1-hour postdose. On Day 4, ECGs were obtained 30 minutes prior to dosing; at 15, 30, 45, 60, 75, 90, 105, 120, 135, 150,

165, 180, 195, 210, 240, 360, and 480 minutes; and 12 and 24 hours after the administration of the study drug.

QT_{CF} was used as the primary assessment and therefore, the analyses of QT_{CF} are the focus of this section.

Analyses of Maximal and Time-Averaged QT_{CF} Intervals

For the maximum postdose QT_{CF} interval, the mean values on Day 1 for febuxostat 80 mg QD, febuxostat 300 mg QD, and moxifloxacin 400 mg were 398.6, 398.5 and 406.8 msec, respectively, as compared with 396.5 msec for placebo. The mean values on Day 4 for febuxostat 80 mg QD, febuxostat 300 mg QD, and moxifloxacin 400 mg QD were 403.7, 405.1 and 415.9 msec, respectively, as compared with 402.9 msec for placebo. Statistically significant regimen effects were observed on both Days 1 and 4 (p<0.001). The mean of the maximum postdose QT_{CF} interval values for moxifloxacin 400 mg was statistically significantly greater than placebo with mean differences from placebo of 10.3 and 13.0 msec (p<0.001) on Days 1 and 4, respectively, while there was no statistically significant difference between either of the febuxostat dose regimens and placebo on either Day 1 or Day 4 (Table 42).

Table 42 (Sponsor's Table 5.3d, ISS) Comparison of Maximum QT_{CF} Intervals (Phase 1 Study C02-023 Part B)

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

QT_{CF} = Fridericia corrected QT interval
p = Statistically significant difference from placebo at the 0.001 level.
Cross-reference: Statistical Table 5.4.1

For the time-averaged postdose QT_{CF} interval, the mean values on Day 1 for febuxostat 80 mg QD, febuxostat 300 mg QD, and moxifloxacin 400 mg QD were 384.9, 385.4, and 389.9 msec, respectively, as compared with 384.1 msec for placebo. The mean values on Day 4 for febuxostat 80 mg QD, febuxostat 300 mg QD, and moxifloxacin 400 mg QD were 383.6, 386.5, and 395.6 msec, respectively, as compared with 384.5 msec for placebo. Statistically significant regimen effects were observed on both Days 1 and 4.

The mean of the time-averaged values for moxifloxacin 400 mg QD was statistically significantly greater than placebo with mean differences from placebo of 5.8 and 11.1 msec (p<0.001) on Day 1 and Day 4, respectively, while there were no statistically significant differences between either of the febuxostat dose regimens and placebo (Table 43).

Table 43 (Sponsor's Table 5.3e, ISS) Comparison of Time-Averaged QT_{CF} Intervals (Phase 1 Study C02-023 Part B)

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

QT_{CF} = Fridericia corrected QT interval
p = Statistically significant difference from placebo at the 0.001 level.
Cross-reference: Statistical Table 5.4.2

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Categorical Analyses of QT_{cf} Intervals

The numbers of subjects with QT_{cf} increases between 30 and 60 msec from baseline to Day 1 were 0, 1 (2%), and 5 (12%) for febuxostat 80 mg QD, febuxostat 300 mg QD, and moxifloxacin 400 mg QD, respectively, as compared with 1 (2%) for placebo.

The numbers of subjects with QT_{cf} increases between 30 and 60 msec from baseline to Day 4 were 3 (7%), 3 (7%), and 19 (46%) for febuxostat 80 mg QD, febuxostat 300 mg QD, and moxifloxacin 400 mg QD, respectively, as compared with 3 (7%) for placebo.

There was 1 subject (Subject 239) with an increase in QT_{cf} for more than 60 msec when dosed with moxifloxacin 400 mg QD on Day 1. No subject in the placebo, febuxostat 80 mg QD, and febuxostat 300 mg QD regimens had an increase in QT_{cf} of more than 60 msec on Day 1. No subject in any regimen had an increase in QT_{cf} of more than 60 msec on Day 4 (Table 44).

Table 44 (Sponsor's Table 5.3f, ISS) Number and Percentage of Subjects with Increases from Baseline to Maximum Postdose QT_{cf} Interval (Phase 1 Study C02-023 Part B)

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

QT_{cf} = Fridericia corrected QT interval
Statistical Table 5.4.5

The numbers of subjects with QT_{cf} shifts to borderline on Day 1 were 0, 2 (5%), and 6 (15%) for febuxostat 80 mg QD, febuxostat 300 mg QD, and moxifloxacin 400 mg QD, respectively, as compared with 0 for placebo (Table 45).

The numbers of subjects with QT_{cf} shifts to borderline on Day 4 were 2 (5%), 4 (10%), and 11 (27%) for febuxostat 80 mg QD, febuxostat 300 mg QD, and moxifloxacin 400 mg QD, respectively, as compared with 2 (5%) for placebo (Table 45).

No subject in any regimen had prolonged QT_{cf} intervals (>450 msec) on either Day 1 or Day 4.

Table 45 (Sponsor's Table 5.3g, ISS) Shifts of QT_{cf} Interval Values from Baseline Relative to the Categories of Normal, Borderline, or Prolonged (Phase 1 Study C02-023 Part B)

Visit	Baseline Category	Placebo (N=41)			Febuxostat 80 mg QD (N=43)			Febuxostat 300 mg QD (N=42)			Moxifloxacin 400 mg (N=41)		
		N	B	P	N	B	P	N	B	P	N	B	P
Day 1	N	39 (95%)	0	0	42 (98%)	0	0	37 (88%)	2 (5%)	0	33 (80%)	6 (15%)	0
	B	2 (5%)	0	0	1 (2%)	0	0	2 (5%)	1 (2%)	0	1 (2%)	1 (2%)	0
	P	0	0	0	0	0	0	0	0	0	0	0	0
Day 4	N	37 (90%)	2 (5%)	0	40 (93%)	2 (5%)	0	34 (82%)	4 (10%)	0	28 (68%)	11 (27%)	0
	B	1 (2%)	1 (2%)	0	1 (2%)	0	0	2 (5%)	1 (2%)	0	1 (2%)	1 (2%)	0
	P	0	0	0	0	0	0	0	0	0	0	0	0

QT_{cf} = Fridericia corrected QT interval
N = Normal (≤430 msec), B = Borderline (>430 to ≤450 msec), and P = Prolonged (>450 msec)
Cross-reference: Statistical Table 5.4.4

Population PK/PD Substudy (C02-009)

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In the Phase 3, randomized, multicenter, double-blind, allopurinol and placebo-controlled, 28-week study (C02-009), 310 subjects at selected sites participated in a population PK/PD substudy.

In the analysis of quantitative ECG variables for subjects participating in the PK/PD substudy, sporadic statistically significant differences were observed between at least 1 of the febuxostat treatment groups and the allopurinol 300/100 mg QD treatment group for the mean change from baseline to 2.5-4.0 hours postdose, Week 28, and/or maximum of post-baseline values in QT interval, heart rate, QT_{cF} interval, and QT_{cB} interval. For QT, QT_{cF}, and QT_{cB} intervals, larger increases were noted at these timepoints for the allopurinol 300/100 mg QD treatment group compared to the febuxostat treatment groups.

Statistically significant differences were observed between at least 1 of the febuxostat treatment groups and the placebo group for the mean change from baseline to the 0.75-2.0 hours postdose in heart rate (increase for febuxostat 80 mg QD compared to decrease for placebo), from baseline to Week 28 in QT_{cF} interval (decrease for febuxostat 240 mg QD compared to increase for placebo), and from baseline to the 0.75-2.0 hours postdose in QT_{cB} interval (increase for febuxostat 240 mg QD compared to decrease for placebo).

Additionally, statistically significant differences were observed between the febuxostat 80 mg QD and febuxostat 240 mg QD treatment groups for the mean change from baseline to Week 28 in QT_{cF} and QT_{cB} intervals, with increases observed in the febuxostat 80 mg QD group and decreases observed in the febuxostat 240 mg QD group.

A statistically significant difference was also observed between the febuxostat 120 mg QD and febuxostat 240 mg QD treatment groups for the mean change from baseline to Week 28 in QT_{cB} interval, with an increase observed in the febuxostat 120 mg QD group and a decrease observed in the febuxostat 240 mg QD group.

Statistically significant differences were also observed between the allopurinol 300/100 mg and placebo treatment groups for the mean change from baseline to the 2.5-4.0 hours postdose, mean of post-baseline values, and maximum of post-baseline values in QT_{cB} interval, with larger increases observed in the allopurinol 300/100 mg QD treatment group (Table 46).

Of note, QT assessments at 0.75-2.0 hours, 2.5-4 hours, and at Week 28 were not done on the same day.

Table 46 (Sponsor's Table 5.3j, ISS)

Statistically Significant Treatment Group Differences in Mean Change from Baseline to the Pharmacokinetic/Pharmacodynamic Substudy Timepoints-ECG Parameters (Phase 3 Study C02-009)

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ECG Parameter (unit)	Placebo			Febuxostat 80 mg QD			Febuxostat 120 mg QD			Febuxostat 240 mg QD			Allopurinol 300/100 mg QD		
	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)
QT Interval (msec)															
Baseline	43	391.2	(41.57)	78	389.8	(33.18)	68	397.8	(35.09)	33	394.2	(39.05)	74	395.5	(35.57)
Mean Δ at 0.75-2.0 Hr	32	-0.2	(29.75)	51	-8.1 ^a	(30.03)	43	-5.5	(29.46)	21	-4.2	(29.44)	55	3.9	(22.60)
Mean Δ at Week 28	37	4.1	(26.48)	65	-1.5 ^a	(26.67)	54	-3.6 ^a	(26.26)	29	-5.6 ^a	(32.24)	65	8.2	(27.84)
Maximum Δ	37	14.5	(23.21)	69	6.9 ^a	(25.51)	56	6.9 ^a	(26.84)	30	6.8	(28.74)	65	17.4	(23.58)
Heart Rate (b/min)															
Baseline	43	70.0	(13.85)	78	69.8	(11.17)	68	67.0	(12.24)	33	71.1	(12.44)	74	69.9	(13.22)
Mean Δ at 0.75-2.0 Hr	32	-1.5	(10.76)	51	3.3 ^h	(11.56)	43	1.6	(11.51)	21	3.9	(7.94)	55	-1.2	(9.67)
QTcF (msec)															
Baseline	43	407.6	(27.46)	78	406.7	(20.23)	68	409.5	(21.96)	33	414.4	(31.78)	74	412.7	(23.31)
Mean Δ at Week 28	37	1.6	(18.56)	65	0.2 ^a	(14.24)	54	-0.5 ^a	(12.75)	29	-6.7 ^h	(19.58)	65	6.3	(15.42)
Maximum Δ	37	8.3	(12.18)	69	7.1 ^a	(13.79)	56	5.8 ^a	(13.46)	30	4.8 ^a	(16.52)	65	12.0	(11.98)
QTcB (msec)															
Baseline	43	416.1	(29.23)	78	415.2	(21.74)	68	415.3	(22.22)	33	424.6	(34.43)	74	421.7	(25.27)
Mean Δ at 0.75-2.0 Hr	32	-3.1	(16.31)	51	2.5	(12.80)	44	0.5	(18.81)	21	7.6 ^a	(15.49)	55	3.0	(13.10)
Mean Δ at 2.5-4.0 Hr	31	-3.1	(11.91)	48	2.2	(10.06)	40	2.7	(12.55)	20	4.0	(16.60)	53	4.4 ^a	(13.45)
Mean Δ at Week 28	37	-0.0	(18.46)	65	1.0 ^a	(14.51)	54	0.9 ^a	(13.70)	29	-7.5 ^a	(19.31)	65	5.1	(16.16)
Mean Δ	37	-1.1	(12.12)	69	2.0	(11.48)	55	1.4	(13.19)	30	-1.1	(16.11)	65	4.0 ^a	(10.22)
Maximum Δ	37	6.3	(12.27)	69	8.8	(14.41)	56	7.4 ^a	(12.78)	30	6.6 ^a	(16.12)	65	13.1 ^a	(13.35)

Hr = hours postdose; QT_F = QT interval (Fridericia correction); QT_{cF} = QT interval (Bazett correction)
p = Statistically significant difference versus placebo (p≤0.05) using ANOVA
a = Statistically significant difference versus allopurinol 300/100 mg QD (p≤0.05) using ANOVA
h = Statistically significant difference versus febuxostat 240 mg QD (p≤0.05) using ANOVA
Cross-reference: Statistical Table 5.6.1

A greater proportion of subjects in the allopurinol 300/100 mg QD treatment group had a QT interval increase from baseline to maximum postdose between 30 and 60 msec (26%) compared to the placebo, febuxostat 80 mg QD, febuxostat 120 mg QD, febuxostat 240 mg QD treatment groups (14%, 13%, 7%, and 17%, respectively). The proportions of subjects with a QT interval increase from baseline to maximum postdose of >60 msec was 85% in each treatment group.

The proportions of subjects with a QT_{cF} increase from baseline to maximum postdose of <30 msec, between 30 and 60 msec, and >60 msec were similar in the 5 treatment groups, with the majority of increases <30 msec. No subject in any treatment group had an increase from baseline to maximum postdose of >60 msec in QT_{cF} interval.

Additionally, a greater proportion of subjects in the allopurinol 300/100 mg QD treatment group had a QT_{cB} interval increase from baseline to maximum postdose between 30 and 60 msec (14%) compared to the placebo, febuxostat 80 mg QD, febuxostat 120 mg QD, and febuxostat 240 mg QD treatment groups (3%, 9%, 5%, and 7%, respectively). No subject in any treatment group had an increase from baseline to maximum postdose of >60 msec in QT_{cB} interval (Table 47).

Table 47 (Sponsor's Table 5.3k, ISS)
Number and Percentage of Subjects with Increases from Baseline to Maximum Postdose QT, QT_{cF}, and QT_{cB} Interval for PK/PD Substudy Subjects (Phase 3 Study C02-009)

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Increase from Baseline	Treatment Group a (%)				
	Placebo (N=37)	Febuxostat 80 mg QD (N=69)	Febuxostat 120 mg QD (N=56)	Febuxostat 240 mg QD (N=30)	Allopurinol 300/100 mg QD (N=65)
QT interval (msec)					
<30 msec	30 (81%)	58 (84%)	49 (88%)	24 (80%)	45 (69%)
30-60 msec	5 (14%)	9 (13%)	4 (7%)	5 (17%)	17 (26%)
>60 msec	2 (5%)	2 (3%)	3 (5%)	1 (3%)	3 (5%)
QT_{cf} interval (msec)					
<30 msec	33 (95%)	65 (97%)	54 (96%)	28 (93%)	60 (92%)
30-60 msec	2 (5%)	4 (6%)	2 (4%)	2 (7%)	5 (8%)
>60 msec	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
QT_{cb} interval (msec)					
<30 msec	36 (97%)	63 (91%)	53 (95%)	28 (93%)	36 (86%)
30-60 msec	1 (3%)	6 (9%)	3 (5%)	2 (7%)	9 (14%)
>60 msec	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

QT_{cf} = QT interval (Friderici correction), QT_{cb} = QT interval (Bazett correction)
Cross-reference: Statistical Table 5.6.3

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Among subjects with a normal (<430 msec) QT interval at baseline, the proportion of subjects who had a shift to borderline (430-450 msec) was highest in the placebo group (11%), followed by the febuxostat 240 mg QD, febuxostat 120 mg QD, allopurinol 300/100 mg QD, and febuxostat 80 mg QD treatment groups (10%, 9%, 9%, and 4%, respectively). Only 3 subjects (1 febuxostat 120 mg QD, 1 febuxostat 240 mg QD, and 1 allopurinol 300/100 mg QD) had a shift from normal to prolonged (>450 msec).

The proportion of subjects who had a shift from normal at baseline to borderline (430-450 msec) in QT_{cf} was low and similar in the 5 treatment groups (5% to 10%). Only 1 subject (allopurinol 300/100 mg QD) had a shift to prolonged (>450 msec) in QT_{cf} interval.

The proportion of subjects who had a shift from normal at baseline to borderline (430-450 msec) in QT_{cb} was highest in the allopurinol 300/100 mg QD group (15%) followed by the febuxostat 240 mg QD, febuxostat 80 mg QD, febuxostat 120 mg QD, and placebo groups (13%, 9%, 5%, and 3%, respectively). Only 4 subjects (1 febuxostat 80 mg QD, 1 febuxostat 120 mg QD, and 2 allopurinol 300/100 mg QD) had a shift from normal to prolonged (>450 msec) in QT_{cb} interval. A greater proportion of subjects in the allopurinol 300/100 mg QD treatment group had a T wave abnormality at 0.75-2.0 hours postdose, 2.5-4.0 hours postdose, and Week 28 compared to subjects in the placebo, febuxostat 80 mg QD, febuxostat 120 mg QD, and febuxostat 240 mg QD treatment groups. The incidence of U wave present was generally comparable among treatment groups at all evaluations (C02-009 CSR).

No clinically significant treatment differences or changes from baseline were observed for any vital sign or weight parameter in the febuxostat Phase 3, continuous exposure in the Phase 2/3, or Phase 1 clinical trials.

In the Phase 2/3 and Phase 1 studies, the majority of subjects had normal 12-lead resting ECGs or experienced ECG changes from baseline that were considered not clinically significant by the investigator.

In the Phase 3 controlled studies, when 12-lead resting ECGs were centrally analyzed, the proportion of subjects with at least 1 ECG coded with MedDRA ranged from 10 to 17% across treatment groups, with the proportion being 17% in the placebo group. No clinically significant treatment difference in the incidence of any specific MedDRA HLT was observed.

In Phase 3 Study C02-009, no clinically significant changes from baseline were observed in mean QT_{cf} or QT_{cb} in any of the treatment groups. The incidence of increases in QT_{cf} and QT_{cb} interval from baseline of 30-60 msec was similar across all treatment groups.

No subject in any treatment group experienced an increase >60 msec of the QT_{CF} or QT_{CB} interval.

In the Phase 1 QT interval Study, C02-023 Part B, subjects were exposed to placebo, febuxostat 80 mg QD, febuxostat 300 mg, or moxifloxacin 400 mg QD (41, 43, 42, and 41 subjects, respectively). There were no statistically significant changes in QT_{CF} and QT_{CB} interval from baseline in the febuxostat 80 mg QD or 300 mg QD treatment groups as compared to placebo. The incidence of increases in QT_{CF} and QT_{CB} intervals from baseline of 30-60 msec was similar between febuxostat 80 mg QD, febuxostat 300 mg QD, and placebo groups. No subject in any febuxostat treatment group experienced a >60 msec increase in QT_{CF} or QT_{CB} interval. Furthermore, in 4 additional Phase 1 studies, no clinically meaningful changes in QT_{CF} and QT_{CB} interval were observed.

Reviewer's comments:

- *Febuxostat 80 mg QD, febuxostat 120 mg QD and febuxostat 240 mg QD appears to have no or little effect on 12-lead resting ECGs.*
- *Febuxostat doses up to 300 mg QD appeared to have no effect on cardiac repolarization, as assessed by the QT_{CF} and QT_{CB} interval.*

7.1.8 Immunogenicity

Not applicable since the drug has no known immunogenic potential

7.1.9 Human Carcinogenicity

Unknown at this time

7.1.10 Special Safety Studies

1 study each conducted in hepatic and renal impaired subjects, safety data from those studies were included in ISS. See ClinPharm review by Lei Zhang, Ph.D. for more details.

7.1.11 Withdrawal Phenomena and/or Abuse Potential

Febuxostat is not belong to a class of drugs with known abuse potential or withdrawal phenomena. No assessment of physiological or psychological dependency has been performed to date. No studies were performed that evaluated rebound or withdrawal effects.

No adverse events that would indicate withdrawal phenomena were identified in the database.

7.1.12 Human Reproduction and Pregnancy Data

One subject became pregnant during the Phase 1 Study TMX-01-009, a bioavailability study. In this study, dosing consisted of 4 single dose regimens separated by a 7-day washout period (Regimen A: febuxostat one 20 mg tablet Teijin formulation; Regimen B: febuxostat one 20 mg

tablet Abbott formulation; Regimen C: febuxostat one 80 mg tablet Abbott formulation; and Regimen D: four 20 mg tablets Abbott formulation). A positive serum pregnancy test result was obtained at the final study visit for a 28-year-old female (Subject 116). This subject became pregnant after receiving 2 doses of febuxostat 80 mg (dosing Regimens D and C) and was subsequently exposed to febuxostat 20 mg for 2 doses (dosing Regimens B and A) after her estimated date of conception, prior to the positive serum pregnancy test. The pregnancy was followed to full-term and the follow-up information revealed that the subject had an uneventful pregnancy and delivered a normal, healthy infant.

Recommendations to the label:

- *There have been no studies in pregnant women*
- *Because many drugs are excreted in human milk, caution should be exercised when febuxostat is administered to a nursing woman.*

b(4)

7.1.13 Assessment of Effect on Growth

Not applicable

7.1.14 Overdose Experience

No deaths were observed in rats following a single oral dose of 300 mg/kg (approximately 27 times the MRHD of 120 mg/day based on body surface area of a 70 kg person), but deaths were observed in rats at 600 mg/kg (approximately 54 times the MRHD based on body surface area of a 70 kg person). The lethal dose in rats is considered to be between 300 – 600 mg/kg (CTD Module 2.6.6).

Oral doses up to 2000 mg/kg in dogs (approximately 598 times the MRHD of 120 mg/day based on body surface area of a 70 kg person) did not produce deaths (CTD Module 2.6.6).

In Part A of Phase 1 Study C02-023, 10 subjects were exposed to febuxostat 300 mg QD (2.5 times the highest recommended dose) for 7 days. The most frequently reported study drug-related adverse events were hot flushes (7 subjects), diarrhea (6 subjects), headache (4 subjects), and dizziness and nausea (3 subjects each). All of the adverse events reported were mild in severity and most were self-limiting. No deaths, serious adverse events, or premature discontinuations due to adverse events were reported. There were no clinically significant changes in ECG, physical findings, or clinical laboratory values.

In Part B of Study C02-023, 43 subjects were randomized to 1 of 4 regimen sequences consisting of 4 regimens within each sequence. Doses studied were placebo, febuxostat 80 mg QD, febuxostat 300 mg QD, and moxifloxacin 400 mg QD each administered for 4 days. The overall incidence of adverse events in the placebo and febuxostat 300 mg QD regimens was 34% and 55%, respectively. The majority of the adverse events reported were mild and self-limiting. The most common study drug-related adverse events were headaches, diarrhea, gastrointestinal and

abdominal pains, nausea and vomiting, feeling hot, and hot flushes/flushing. A higher number of possibly or probably related adverse events were seen with the **febuxostat 300 mg QD** regimen than with any other regimen. These events were primarily **diarrhea, feeling hot, and headache**. One subject who completed the study developed a mild rash on the left thigh after 4 days of receiving febuxostat 300 mg QD. The event resolved without treatment on Day 41 and the investigator considered the event possibly related to study drug. There were no deaths or other serious adverse events.

In Phase 3 Study C02-009, 134 subjects received febuxostat **240 mg QD** (twice the highest recommended dose) for 28 weeks. The incidence of treatment-emergent adverse events in the febuxostat 240 mg QD group (73%) was similar to that in placebo group (72%).

7.1.15 Postmarketing Experience

Not applicable since Febuxostat is not approved for marketing in any country at this time.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Please, see medical officer review by Dr. Schiffenbauer, Section 4.

The United States clinical program for febuxostat included 24 Phase 1 trials (including 1 study each conducted in hepatic and renal impaired subjects), 2 Phase 2 trials (including 1 dose-ranging study), and 3 Phase 3 trials in subjects with a history or presence of gout and a serum urate level ≥ 8.0 mg/dL.

Table 48 (Sponsor's Table 13.1a, ISS)

Description of Clinical Efficacy and Safety Studies - Controlled Studies

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Study ID/ No. of Centers/ Locations	Study Start Enrollment Status, Date Total Enrollment/ Enrollment Goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm Entered/ Completed	Duration	Gender M/F Mean Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
Pivotal Studies									
C02-009/167/ United States	21/Feb/2003 Completed 7/Apr/2004 1072/1000	Randomized, double-blind, parallel-group, positive- and placebo- controlled	Placebo PO Febuxostat: 80 mg QD PO 120 mg QD PO 240 mg QD PO Allopurinol 300/100 mg QD PO	To compare the safety and efficacy of different oral doses of febuxostat versus placebo and allopurinol in subjects with gout	134/101 267/174 269/200 134/86 268/211	28 weeks	123/11; 51.5 (26-82) 251/16; 50.6 (22-84) 256/13; 51.2 (26-81) 126/8; 54.3 (30-82) 249/19; 51.8 (24-84)	Male or female subjects between 18 and 85 years of age, inclusive, with hyperuricemia defined as a serum urate level of ≥8.0 mg/dL on the Day -2 Visit	The proportion of subjects whose last 3 serum urate levels were ≥6.0 mg/dL.

PO = oral; QD = once daily; ARA = American Rheumatism Association

- a Allopurinol 300 mg QD for subjects with serum creatinine ≤1.5 mg/dL at Day -2 or 100 mg QD for subjects with serum creatinine >1.5 mg/dL and ≤2.0 mg/dL at Day -2.
- b Allopurinol 300 mg QD for subjects with serum creatinine ≤1.5 mg/dL or 100 mg QD for subjects with serum creatinine >1.5 mg/dL and ≤2.0 mg/dL at the visit prior to the last visit from the previous study (C02-009 or C02-010).

Study ID/ No. of Centers/ Locations	Study Start Enrollment Status, Date Total Enrollment/ Enrollment Goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm Entered/ Completed	Duration	Gender M/F Mean Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
Pivotal Studies (continued)									
C02-010/112/ United States and Canada	11/Jul/2002 Completed 20/Feb/2004 760/750	Randomized, double-blind, parallel-group, positive- controlled	Febuxostat 80 mg QD PO 120 mg QD PO Allopurinol 300 mg QD PO	To compare the safety and efficacy of febuxostat vs. allopurinol in subjects with gout	256/168 251/153 253/187	52 weeks	243/13; 51.8 (25-81) 243/8; 52.0 (23-81) 243/10; 51.6 (24-83)	Male or female subjects between 18 and 85 years of age, inclusive, with hyperuricemia defined as a serum urate level of ≥8.0 mg/dL at the Day -2 Visit; history or presence of gout defined by the ARA Criteria for Diagnosis of Gout.	The proportion of subjects whose last 3 serum urate levels were ≥6.0 mg/dL.

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Study ID/ No. of Centers/ Locations	Study Start Enrollment Status, Date Total Enrollment/ Enrollment Goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm Entered/ Completed	Duration	Gender M/F Mean Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
Supportive Studies (continued)									
TMC-09-094 24/United States	31/Jan/2001 Completed	Randomized, double-blind, placebo- controlled, parallel-design, dose-response	Placebo PO	To select oral dose(s) of febuxostat which safely and effectively decrease serum urate levels in subjects with gout	38/36	4 weeks	32/6: 52.4 (33-76)	Male and female subjects between 18 and 85 years of age, inclusive, with hyperuricemia, defined as a serum urate level of ≥ 8.0 mg/dL at the Day -2 Visit. Subjects also had a history or presence of gout, as defined by the ARA criteria	The proportion of subjects whose serum urate level decreased to ≤ 6.0 mg/dL after treatment with study drug (Day 28).
	02/Jul/2001		Febuxostat 40 mg QD PO		37/36		33/4: 52.2 (21-80)		
	153/129		80 mg QD PO		40/37		38/2: 55.2 (29-78)		
			120 mg QD PO		38/36		33/5: 56.2 (34-76)		
Supportive Studies									
CO2-021-173 United States and Canada	28/Jul/2003 Ongoing (30/Apr/2004 for interim analysis) 1674/1500	Randomized, open-label, positive- controlled, safety extension	Febuxostat: 80 mg QD PO 120 mg QD PO Allopurinol 300/100 mg QD PO	To evaluate the long- term safety of febuxostat 80 mg QD and 120 mg QD doses required to reduce serum urate levels to ≤ 6.0 mg/dL in subjects with gout, as compared to allopurinol	Entered/ ongoing: 650 282 142	2 years	626/24: 51.1 (24-84) 267/15: 51.1 (24-84) 138/4: 51.1 (29-83)	Subjects who completed CO2-009 or CO2-010.	The proportion of subjects whose serum urate level decreased to ≤ 6.0 mg/dL.

Table 49 (Sponsor's Table 13.1b, ISS)
Description of Clinical Efficacy and Safety Studies - Uncontrolled Studies

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Study ID/ No. of Centers/ Locations	Study Start Enrollment Status, Date Total Enrollment/ Enrollment Goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm Entered/ Completed	Duration	Gender M/F Mean Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
Supportive Studies									
TMX-01-003/ 23 United States	21/Mar/2001 Ongoing (15/Sep/2003 for interim analysis) 120/116	Open-label	Febuxostat: 40 mg QD PO 80 mg QD PO 120 mg QD PO	To evaluate the long-term safety of febuxostat at doses expected to maintain serum urate levels within clinically acceptable levels in subjects with gout who had completed Study TMX-00-004 over an intended 5-year period	Entered/ ongoing: 10/8 83/47 23/12	5 years	10/0; 53.3 (35-66) 74/9; 53.8 (23-76) 21/2; 51.3 (31-78)	Subjects who completed TMX-00-004	The proportion of subjects whose serum urate level decreased to or was maintained at $\leq$ 8.0 mg/dL

PO = oral; QD = once daily; BID = twice daily; PK = pharmacokinetic; PD = pharmacodynamic; BA = bioavailability; HCTZ = hydrochlorothiazide
 b Date of last study procedure.

Study ID/ No. of Centers/ Locations	Study Start Enrollment Status, Date Total Enrollment/ Enrollment Goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm Entered/ Completed	Duration	Gender M/F Mean Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
Phase I (Pharmacokinetic) Studies									
TMX-99-001/ 2 United States	7/Nov/1999 Completed 15/Apr/2001 154 up to 96	Randomized, double-blind, placebo- controlled, multiple-dose, dose-escalation	Placebo PO Febuxostat 10 mg QD PO 20 mg QD PO 30 mg QD PO 40 mg QD PO 50 mg QD PO 70 mg QD PO 90 mg QD PO 120 mg QD PO 160 mg QD PO 180 mg QD PO 240 mg QD PO 30 mg BID PO	To assess the safety of febuxostat; determine the maximum tolerated dose of febuxostat; and determine the PK and PD profiles of febuxostat following oral administration of multiple daily doses over a range of doses and regimens (e.g. QD and/or BID)	26/23 10/10 10/0 10/0 8/8 10/10 10/10 10/10 10/9 10/10 10/7 10/8 10/10	13 days	16/10 33.3 (20-51) 8/2 27.5 (19-36) 5/5 30.2 (19-39) 6/4 35.1 (19-44) 5/3 39.4 (25-53) 9/11 34.9 (20-54) 5/5 32.3 (19-52) 5/5 31.4 (19-45) 5/5 33.8 (20-49) 4/6 32.6 (19-53) 6/4 31.5 (21-49) 5/5 29.8 (20-50) 8/2 28.1 (21-44)	Healthy male and female subjects between 18 and 55 years of age, inclusive	PK evaluations of febuxostat and metabolites (D, serum and urine levels of uric acid, xanthine, and hypoxanthine)
TMX-00-002/ 1 United States	19/Aug/2000 Completed 27/Aug/2000* 24/24	Randomized, single-dose, 2-period crossover	• Febuxostat 40 mg PO under fasting conditions • Febuxostat 40 mg PO under fed conditions	To compare the BA under fasting and non-fasting conditions of febuxostat in healthy subjects given a single 40-mg dose	24/24 23/23	2 single doses separated by 7 days	11/13 40.0 (22-54)	Healthy male and female subjects between 18 and 55 years of age, inclusive	PK evaluations of febuxostat under fasting and nonfasting conditions

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Study ID/ No. of Centers/ Locations	Study Start Enrollment/ Status, Date Total Enrollment/ Enrollment Goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm Entered/ Completed	Duration	Gender M/F Mean Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
Phase I (Pharmacokinetic) Studies									
TMX-00-003/ 1/United States	27/Jun/2000 Completed 10/Jun/2008 64/64	Randomized, investigator- blind, placebo- controlled, multiple-dose, parallel-group	Placebo PO Febuxostat 10 mg BID PO 20 mg QD PO 40 mg QD PO	To assess the safety, PK parameters and PD effects of Febuxostat in hyperuricemic subjects receiving either 10 mg BID, 20 mg QD, or 40 mg QD of Febuxostat or placebo	16/16 16/16 16/15 16/14	14 days	4/12 52.6 (36-77) 9/7 47.2 (30-69) 11/5 47.3 (31-82) 11/5 50.9 (31-82)	Male and female subjects between 30 and 85 years of age, inclusive, with a history of hyperuricemia and a uric acid level of 8.0- 12.0 mg/dl, (unconfirmed at baseline), an estimated creatinine clearance of ≥50 ml/ minute, and no history of xanthine or gout	PK: evaluations of Febuxostat PD: serum and urine levels of uric acid, xanthine, and hypoxanthine
Phase I (Pharmacokinetic) Studies									
TMX-00-006/ 1/United States	2/Nov/2000 Completed 16/Nov/2003 22/24	Randomized, open-label, multiple-dose, 2-period crossover	Febuxostat 40 mg QD PO from Day 1 to Day 7 with colchicine 0.6 mg BID PO from Day 4 to 7 Febuxostat 40 mg QD PO from Day 1 to Day 7	To evaluate the effect of colchicine on the PK profile of Febuxostat after multiple doses of both compounds	22/22 22/22	14 consecu- tive days (7 days/ period)	16/6 36.0 (19-53)	Healthy male and female subjects between 18 and 55 years of age, inclusive	PK: evaluations of Febuxostat and the effect of colchicine on the PK of Febuxostat
Phase I (Pharmacokinetic) Studies									
TMX-01-008/ 3/United States	16/May/2001 Completed 18/Dec/2001 32/32	Open-label, multiple-dose, parallel-group	Febuxostat 80 mg QD PO • normal renal function • mild renal impairment • moderate renal impairment • severe renal impairment	To evaluate the safety, PK, and PD profile of Febuxostat after 7 consecutive days of 80 mg QD dosing in subjects with varying degrees of renal impairment and subjects with normal renal function	11/11 6/6 7/7 8/7	7 days	8/3, 52.5 (35-68) 2/4, 51.2 (26-65) 3/4, 54.3 (40-70) 5/3, 55.8 (45-76)	Male and female subjects between 30 and 70 years of age, inclusive, with normal renal function or varying degrees of renal impairment; groups balanced by gender and age	PK: evaluations of Febuxostat and its metabolites 67M-1, 67M-2, and 67M-4 on Day 7 PD: serum and urine levels of uric acid, xanthine, and hypoxanthine

Study ID/ No. of Centers/ Locations	Study Start Enrollment Status, Date Total Enrollment/ Enrollment Goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm Entered/ Completed	Duration	Gender M/F Mean Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
Phase I (Pharmacokinetic) Studies									
TMX-01-009/ 1/United States	5/30/2001 Completed 26/June/2001 30/32	Randomized, open-label, single-dose, 4-period crossover	Febuxostat 20 mg PO • manufactured by Teijin Ltd. • manufactured by Abbott Febuxostat 80 mg PO • manufactured by Abbott Febuxostat 4 x 20 mg • manufactured by Abbott	1) to provide a comparison of the BA of febuxostat from 20 mg febuxostat tablets manufactured at Abbott relative to the 20 mg febuxostat tablets manufactured at Teijin; 2) to investigate dose proportionality of febuxostat from 20 mg to 80 mg; and 3) to determine the BA of febuxostat from 4 x 20 mg tablets relative to an 80-mg tablet manufactured at Abbott	28/29 29/29 28/28 29/29	4 single doses each separated by 7 days	16/14 35.0 (18-55)	Healthy male and female subjects between 18 and 55 years of age, inclusive	PK: evaluations of the febuxostat tablets manufactured at different sites
Phase I (Pharmacokinetic) Studies									
TMX-01-010/ 1/United States	10/Jan/2001 Completed 1/Jul/2001 28/32	Randomized, open-label, single-dose, 4-period crossover	• Febuxostat 20 mg PO Abbott formulation A • Febuxostat 20 mg PO Abbott formulation B • Febuxostat 80 mg PO Abbott formulation B • Febuxostat 4 x 20 mg PO Abbott formulation B	To provide a comparison of the BA of febuxostat from 20 mg formulation B febuxostat tablets manufactured at Abbott relative to the 20 mg febuxostat formulation A tablets manufactured at Abbott; to investigate dose proportionality of febuxostat formulation B from 20 mg to 80 mg; and determine the BA of 80 mg febuxostat formulation B tablets relative to 4 x 20 mg febuxostat formulation B tablets manufactured at Abbott	28/28 28/28 27/27 27/27	4 single doses each separated by 7 days	22/6 30.8 (18-52)	Healthy male and female subjects between 18 and 55 years of age, inclusive	PK: evaluations of the febuxostat tablets manufactured at different sites

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Study ID/ No. of Centers/ Locations	Study Start Enrollment Status, Date Total Enrollment/ Enrollment Goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm Entered/ Completed	Duration	Gender M/F Mean Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
Phase I (Pharmacokinetic) Studies									
EMX-01-012 2/United States	12-Sep-2001 Completed 13/13 28/24-32	Open-label, multiple-dose, parallel-group	Febuxostat 80 mg QD PO • normal hepatic function • mild hepatic impairment • moderate hepatic impairment	To compare the safety, PK, and PD profile of febuxostat in subjects with hepatic impairment to subjects with normal hepatic function	12/12 8/8 8/8	7 days	6/6: 50.3 (39-60) 4/4: 52.9 (47-62) 5/3: 50.4 (42-59)	Male and female subjects between 30 and 70 years of age, inclusive, with normal hepatic function and varying degrees of hepatic impairment. The normal hepatic function group was to be balanced with the impaired hepatic function groups according to gender, weight and age	PK: evaluations of febuxostat and its metabolites 67M-1, 67M-2, and 67M-4 on Day 7 PK: serum and urine levels of uric acid, xanthine, and hypoxanthine

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Study ID/ No. of Centers/ Locations	Study Start Enrollment Status, Date Total Enrollment/ Enrollment Goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm Entered/ Completed	Duration	Gender M/F Mean Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
Phase I (Pharmacokinetic) Studies									
TMX-01-014/ 1/United States	17/Oct/2001 Completed 24/Oct/2001 24/24	Randomized, open-label, single-dose, 2-period crossover	- Febuxostat 80 mg PO and antacid (magnesium hydroxide/aluminum hydroxide) 20 ml, PO - Febuxostat 80 mg PO	To evaluate the effect of an antacid on the PK of febuxostat in healthy subjects	14/24 14/24	2 single doses separated by 7 days	10/14 36.0 (19-53)	Healthy male and female subjects between 18 and 55 years of age, inclusive	PK: evaluations of febuxostat alone and with antacid
TMX-01-016/ 1/United States	5/Dec/2001 Completed 22/Dec/2001 18/48	Open-label, multiple-dose, parallel-group	- Febuxostat 80 mg QD PO - aged 18-40 years inclusive and male - aged 18-40 years inclusive and female - aged ≥65 years and male - aged ≥65 years and female	To evaluate the effect of gender and age on the safety, PD and PK of febuxostat when administered for 7 consecutive days	12/12 12/12 12/12 12/12	7 days	12/0: 30.8 (19-40) 0/12: 32.8 (22-40) 12/0: 71.7 (65-76) 0/12: 68.2 (65-74)	Healthy, male and female subjects between 18 and 40 years of age, inclusive, or ≥65 years of age	PK: evaluations of febuxostat and its metabolites (7M-1, 67M-2 and 67M-4) P1: serum and urine levels of uric acid, xanthine and hypoxanthine
Phase I (Pharmacokinetic) Studies									
TMX-02-017/ 1/United States	21/Feb/2002 Completed 12/Mar/2002 27/27	Randomized, open-label, multiple-dose, 3-period crossover	- Febuxostat 80 mg QD PO - Febuxostat 80 mg QD PO & indomethacin 50 mg BID PO - Indomethacin 50 mg BID PO	To assess the potential effect of indomethacin on the PK of febuxostat and the potential effect of febuxostat on the PK of indomethacin at steady state in healthy subjects	26/26 27/27 26/26	5 days per period separated by 40 hours	13/14 36.7 (21-52)	Healthy male and female subjects between 18 and 55 years of age, inclusive	PK: evaluations of both febuxostat and indomethacin
TMX-02-018/ 1/United States	23/Feb/2002 Completed 16/Mar/2002 28/28	Randomized, open-label, single-dose, 4-period crossover	- Febuxostat 20 mg PO - Teijin Ltd. febuxostat coated tablets to Teijin 20 mg PO Abbott B1 80 mg PO Abbott B1 4 x 20 mg PO Abbott B1	To compare the BA of Abbott Formulation B1 febuxostat coated tablets to Teijin febuxostat tablets; to assess the BA of febuxostat Formulation B1 4 x 20 mg coated tablets relative to 80 mg Formulation B1 coated tablets manufactured by Abbott; and dose proportionality from 20 mg to 80 mg	28/28 26/26 17/27 26/26	4 single doses each separated by 6 days	14/14 26.8 (18-50)	Healthy male and female subjects between 18 and 55 years of age, inclusive	PK: evaluations of the febuxostat tablets manufactured at different sites

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Study ID/ No. of Centers/ Locations	Study Start Enrollment Status, Date Total Enrollment/ Enrollment Goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm Entered/ Completed	Duration	Gender M/F Mean Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
Phase I (Pharmacokinetic) Studies									
E02-0051/ United States	19/Apr/2002 Completed 6/Jun/2002 22/20	Randomized, double-blind, placebo- controlled, multiple-dose, 2- period crossover	- Febuxostat 120 mg QD PO from Day 1 to Day 9, with desipramine 25 mg PO on Day 6 - Placebo for febuxostat 120 mg QD PO from Day 1 to Day 9, with desipramine 25 mg PO on Day 6	To determine the effect of febuxostat on the PK of desipramine, a CYP2D6 substrate, in healthy subjects	22/20 20/20	9 days per period separated by 6 days	10/12 33.7 (19-51)	Healthy male and female subjects between 18 and 55 years of age, inclusive	PK: evaluations of desipramine and 2-hydroxy-desipramine and trough plasma concentrations for febuxostat
E02-0061/ United States	12/Apr/2002 Completed 19/Mar/2002 33/33	Randomized, double-blind, multiple-dose, 3- period crossover	- Febuxostat 120 mg QD PO & colchicine 0.6 mg BID PO - Placebo for febuxostat PO & colchicine 0.6 mg BID PO - Febuxostat 120 mg QD PO	To evaluate the effect of febuxostat on the PK of colchicine at steady state in healthy subjects and to assess the safety of concomitant use of both drugs	33/33 29/28 29/28	14 days per period separated by 14 days	19/14 33.2 (18-45)	Healthy male and female subjects between 18 and 55 years of age, inclusive	PK: evaluations of colchicine in each regimen
Phase I (Pharmacokinetic) Studies									
E02-0131/ United States	17/May/2002 Completed 30/Jun/2002 27/27	Randomized, open-label, multiple-dose, 3- period crossover	- Febuxostat 80 mg QD PO - Febuxostat 80 mg QD PO & naproxen 500 mg BID PO - Naproxen 500 mg BID PO	To assess the potential effect of naproxen on the PK of febuxostat and the potential effect of febuxostat on the PK of naproxen at steady state in healthy subjects	25/25 26/26 27/25	7 days per period separated by 7 days	12/15 38.7 (21-53)	Healthy male and female subjects between 18 and 55 years of age, inclusive	PK: evaluations of febuxostat and naproxen
E02-023 (Part A)/ United States	8/Aug/2002 Completed 13/Aug/2002 12/12	Randomized, double-blind, placebo- controlled, multiple-dose	Placebo PO Febuxostat 360 mg QD PO	To assess the safety of febuxostat 360 mg QD in healthy subjects and to determine the PK (PD) for febuxostat 100 mg QD in healthy subjects	12/12 10/10	7 days	20/9 54.0 (32-66) 3/6 48.8 (26-61)	Healthy male and female subjects between 25 and 65 years of age, inclusive	PK: evaluations of febuxostat and its metabolites 57M-1, 57M-2, 57M-4 and unbound fraction of febuxostat in pre-dose plasma samples PD: serum and urine levels of uric acid, xanthine, and hypoxanthine

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Study ID/ No. of Centers/ Locations	Study Start Enrollment Status, Date Total Enrollment/ Enrollment Goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm Entered/ Completed	Duration	Gender M/F Mean Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
Phase I (Pharmacokinetic) Studies									
C02-023 (Part B) 2/ United States	27/Aug/2002 Completed 9/Oct/2002 14/44	Randomized, double-blind, placebo- controlled, multiple-dose, 1-period crossover	- Placebo PO - Febuxostat 300 mg QD PO - Febuxostat 80 mg QD PO - Mexidilone 400 mg QD PO	To assess the potential for a prolongation of the QTc interval after multiple doses of febuxostat in healthy subjects	11/41 12/41 13/43 41/41	4 days per period each separated by 7 days	32/12 41.2 (25-65)	Healthy male and female subjects between 25 and 65 years of age, inclusive	PK: evaluation of both febuxostat doses and Mexidilone
C02-033-1/ United States	15/Dec/2002 Completed 22/Dec/2002 36/36	Randomized, open-label, single-dose, 2-period crossover	- Febuxostat 80 mg PO Formulation B1 - Febuxostat 2 x 40 mg PO Formulation B1	To assess the BA of febuxostat from two 40 mg Formulation B1 tablets relative to one 80 mg Formulation B1 tablet	35/35 36/36	2 single doses separated by 7 days	18/18 28.5 (19-30)	Healthy male and female subjects between 18 and 55 years of age, inclusive	PK: evaluation of both febuxostat regimens
C02-034-1/ United States	13/Dec/2002 Completed 20/Dec/2002 36/36	Randomized, open-label, single-dose, 2- period crossover	- Febuxostat 80 mg PO [redacted] batch size - Febuxostat 80 mg PO [redacted] batch size	To assess the BA of febuxostat from an 80 mg [redacted] batch size) tablet relative to an 80 mg [redacted] batch size) tablet	36/36 36/36	2 single doses separated by 7 days	10/26 43.0 (18-54)	Healthy male and female subjects between 18 and 55 years of age, inclusive	PK: evaluation of both febuxostat regimens
Phase I (Pharmacokinetic) Studies									
C02-036-1/ United States	18/Dec/2002 Completed 13/Jan/2003 24/24	Randomized, open-label, multiple-dose, 2-period crossover	- Febuxostat 80 mg QD PO under fasting conditions - Febuxostat 80 mg QD PO under fed conditions	To determine the effect of food on the PK and PD of febuxostat in healthy subjects following multiple QD oral dosing with febuxostat 80 mg for 6 days	24/24 23/23	6 days per period separated by at least 7 days	15/9 38.6 (20-55)	Healthy male and female subjects between 18 and 55 years of age, inclusive	PK: evaluation of febuxostat PD: 24-hour mean serum urate concentration on both Day -1 and Day 6 of each period and the percent change of 24-hour mean serum urate concentration from Day -1 to Day 6 of each period

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Study ID/ No. of Centers/ Locations	Study Start Enrollment Status, Date Total Enrollment/ Enrollment Goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Arm Entered/ Completed	Duration	Gender M/F Mean Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
Phase I (Pharmacokinetic) Studies									
C03-040-1/ United States	23/Jul/2003 Completed 23/Jul/2003 8/6	Single-dose, open-label	¹⁴ C] febuxostat 80 mg PO	To investigate the metabolism and excretion of radio- labeled febuxostat (¹⁴ C] febuxostat) in subjects receiving a single 80-mg oral dose	5/5	single dose	6:0 27.5 (20-45)	Healthy male subjects between 18 and 55 years of age, inclusive	PK: total radioactivity and febuxostat concentrations in plasma; urine and fecal total radioactivity and excretion; and plasma, urine and fecal metabolic pattern data
Phase I (Pharmacokinetic) Studies									
C03-044-1/ United States	26/Jul/2003 Completed 09/Aug/2003 16/36	Randomized, open-label, single-dose, 2-period crossover	Febuxostat • 120 mg PO formulation B1 • 80 mg PO & 40 mg PO formulation B1	To assess the relative BA of oral febuxostat Formulation B1 120 mg tablet to that from oral Formulation B1 80 mg tablet plus oral Formulation B1 40 mg tablet	35/35 36/36	2 single doses separated by at least 6 days	21:15 32.0 (18-53)	Healthy male and female subjects between 18 and 55 years of age, inclusive	PK: evaluation of both febuxostat regimens
C03-054-1/ United States	09/Jun/2004 Completed 16/Jun/2004 20/20	Randomized, open-label, single-dose, 2-period crossover	Febuxostat 120 mg PO • under fasting conditions • under fed conditions	To determine the effect of food on the PK of febuxostat in healthy subjects following a single dose with one 120 mg oral tablet of febuxostat	19/19 20/20	2 single doses separated by 7 days	9:11 37.4 (19-54)	Healthy male and female subjects between 18 and 55 years of age, inclusive	PK: evaluation of both febuxostat regimens
C03-057-1/ United States	11/Jun/2004 (first dose of warfarin) 07/Feb/2004 (first dose of febuxostat and warfarin) Completed 28/Mar/2004 22/20	Randomized, double-blind, placebo- controlled, multiple-dose, 2- period crossover	Maintenance dose of warfarin QD on Days 1 through 14 with febuxostat 120 mg PO Maintenance dose of warfarin QD on Days 1 through 14 with placebo PO	To determine the effect of multiple doses of febuxostat on the PK and PD of warfarin in healthy male and female subjects following multiple oral doses of warfarin	22/13	0-day warfarin lead-in followed by 2 consecutive 14-day treatment periods	21:1 33.0 (19-53)	Healthy male and female subjects between 18 and 60 years of age, inclusive	PK: evaluations of both febuxostat and R- and S-warfarin
Phase I (Pharmacokinetic) Studies									
C03-059-1/ United States	2/Feb/2004 Completed 15/Feb/2004 16/36	Randomized, open-label, single-dose, 2-period crossover	Febuxostat 80 mg PO & ECITZ, 50 mg PO Febuxostat 80 mg PO	To evaluate the effect of ECITZ on the PK and PD of febuxostat in healthy subjects	30/33	2 single doses separated by at least 7 days	20:16 32.6 (19-51)	Healthy male and female subjects between 18 and 55 years of age, inclusive	PK: evaluation of both febuxostat regimens PD: serum uric acid

7.2.1.1 Study type and design/patient enumeration

Please, also see Section 4 of Dr. Schiffenbauer review, and Section 7.2.1 above.

7.2.1.2 Demographics

The extent of exposure, demographic, and baseline characteristics were summarized for Phase 1 studies, Phase 2/3 studies, Phase 3 controlled studies, and subjects with continuous exposure in Phase 2/3 studies. The extent of exposure was also summarized across all Phase 1/2/3 studies and by study category.

Table 50
Demographic and Baseline Characteristics in Phase 1 Studies

Variable	Febuxostat	Febuxostat	Febuxostat
	Single Dose Studies (N=304)	Multiple Dose Studies (N=507)	All Studies (N=811)
Gender			
Male	157 (51.6%)	295 (58.4%)	452 (55.9%)
Female	147 (48.4%)	211 (41.6%)	359 (44.1%)
Race			
Asian	1 (0.1%)	10 (2.0%)	11 (1.4%)
Black	30 (9.9%)	52 (10.3%)	82 (10.1%)
Caucasian	181 (59.5%)	274 (54.0%)	455 (56.1%)
Hispanic	81 (26.6%)	158 (31.2%)	239 (29.4%)
Other	1 (0.3%)	3 (0.6%)	4 (0.5%)
Age (yr) #			
<45	232 (76.3%)	334 (65.9%)	566 (69.8%)
45-55	72 (23.7%)	141 (27.8%)	213 (26.3%)
>55	0	32 (6.3%)	32 (3.9%)
N	304	507	811
Mean	33.5	39.8	37.6
SD	10.26	13.69	12.05
Median	33.0	38.0	37.0
Min-Max	18-55	18-92	18-92
Single dose studies: TMX-00-002, TMX-01-003, TMX-01-010, TMX-01-014, TMX-02-018, C02-023, C02-034, C03-040, C03-044, C03-050, and C03-059. Multiple dose studies: TMX-00-001, TMX-00-003, TMX-00-006, TMX-01-008, TMX-01-012, TMX-01-016, TMX-02-017, C02-025, C02-026, C02-027, C02-028, C02-035, and C03-057.			
* At baseline			
Variable	Febuxostat	Febuxostat	Febuxostat
	Single Dose Studies (N=304)	Multiple Dose Studies (N=507)	All Studies (N=811)
Weight (lb) #			
<125	25 (7.6%)	24 (4.7%)	47 (5.8%)
125-175	184 (60.2%)	301 (59.4%)	485 (59.8%)
>175	87 (28.6%)	182 (35.9%)	269 (33.2%)
N	304	507	811
Mean	150.1	167.8	164.9
SD	24.94	28.69	27.71
Median	158.9	165.0	162.0
Min-Max	101-240	88-275	89-275
Height (in) #			
N	304	507	811
Mean	66.9	66.9	66.9
SD	3.64	3.93	3.82
Median	67.0	67.0	67.0
Min-Max	58-77	56-75	56-77

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Variable	Febuxostat	Febuxostat	Febuxostat
	Single Dose Studies (N=384)	Multiple Dose Studies (N=507)	All Studies (N=891)
Body Mass Index (kg/m ²) †			
<18.5	3 (1.0%)	5 (1.0%)	8 (1.0%)
18.5-25	146 (48.0%)	187 (36.9%)	333 (37.4%)
25-30	148 (48.7%)	259 (51.1%)	407 (45.7%)
>30	7 (2.3%)	56 (11.0%)	63 (7.0%)
N	384	507	891
Mean	25.66	25.29	25.93
SD	2.907	3.606	3.411
Median	25.12	26.14	25.74
Min-Max	17.2-31.2	17.2-43.2	17.2-43.2

Reviewer's comments:

- In all Phase 1 studies, 56% of the subjects were male and 56% were Caucasian. Subjects ranged in age from 18 to 82 years, with a mean age of 37.6 years. The mean weight was 165 pounds. The mean BMI for all subjects was 25.8 kg/m² and 91% had a BMI between 18.5 and <30 kg/m².

Table 51 (Sponsor's Table 2.4a, ISS)
Demographic and Baseline Characteristics in Phase 2/3 Studies

Variable	Placebo (N=172)	Febuxostat					Aloprurinol (N=629)
		All Doses (N=1707)	40 mg QD (N=46)	80 mg QD (N=1180)	120 mg QD (N=876)	240 mg QD (N=134)	
Gender							
Female	17 (10%)	50 (3%)	4 (9%)	61 (5%)	42 (5%)	8 (6%)	32 (5%)
Male	155 (90%)	1617 (95%)	42 (91%)	1119 (95%)	834 (95%)	126 (94%)	597 (95%)
Race							
Caucasian	140 (81%)	1553 (79%)	40 (87%)	932 (79%)	701 (80%)	107 (80%)	480 (76%)
Black	12 (7%)	163 (10%)	4 (9%)	116 (10%)	78 (9%)	13 (10%)	63 (10%)
Hispanic	11 (6%)	100 (6%)	1 (2%)	68 (6%)	52 (6%)	8 (6%)	45 (7%)
Asian	3 (2%)	43 (3%)	0	31 (3%)	22 (3%)	1 (1%)	16 (3%)
Other	6 (3%)	48 (3%)	1 (2%)	33 (3%)	23 (3%)	5 (4%)	25 (4%)
Age (years)							
<45	48 (28%)	494 (29%)	10 (22%)	348 (30%)	267 (30%)	33 (25%)	199 (32%)
45 to 65	101 (59%)	974 (57%)	26 (57%)	673 (57%)	501 (57%)	77 (57%)	349 (56%)
>65	23 (13%)	239 (14%)	10 (22%)	159 (14%)	108 (12%)	24 (18%)	81 (13%)
Mean (SD)	51.7 (12.25)	51.8 (12.10)	52.4 (13.38)	51.5 (11.93)	51.1 (11.97)	54.3 (12.83)	51.5 (12.21)
Range	26-82	22-84	23-80	22-84	23-84	30-82	24-84
Weight (pounds)^a							
Mean (SD)	216.5 (41.22)	225.9 (44.85)	218.2 (31.43)	226.1 (43.86)	228.9 (46.68)	227.2 (49.04)	226.4 (45.83)
Range	123-360	123-468	170-277	123-425	136-468	139-425	136-468
Height (inches)^a							
N	172	1701	46	1180	873	134	625
Mean (SD)	69.2 (3.68)	69.7 (3.23)	70.0 (3.42)	69.8 (3.25)	69.8 (3.17)	69.7 (3.58)	69.6 (3.36)
Range	47-76	59-83	62-80	59-80	59-80	61-83	59-79
BMI (kg/m²)^a							
N	172	1701	46	1180	873	134	625
18.5 to <25	16 (9%)	87 (5%)	3 (7%)	61 (5%)	38 (4%)	9 (7%)	27 (4%)
25 to <30	61 (35%)	543 (32%)	16 (35%)	370 (31%)	274 (31%)	42 (31%)	214 (34%)
≥30	95 (55%)	1072 (63%)	27 (59%)	749 (63%)	561 (63%)	83 (62%)	384 (61%)
Mean (SD)	31.9 (6.01)	32.7 (6.05)	31.4 (4.55)	32.6 (5.95)	32.9 (6.09)	32.8 (6.55)	32.8 (6.21)
Range	21.8-53.2	20.3-64.6	24.1-42.6	20.3-64.6	20.7-63.5	21.0-64.6	19.6-64.6

SD = standard deviation
Phase 2/3 studies included: TMX-00-004, TMX-01-005, C02-009, C02-010, and C02-021.
a At baseline.
Cross-reference: Statistical Table 2.3.2

No clinically relevant differences were observed across treatment groups in any demographic or baseline characteristic in the Phase 2/3 studies. However, slightly lower mean body weights were observed in the placebo and febuxostat 40 mg QD groups (216.5 and 218.2 pounds, respectively) compared to the febuxostat 80 mg QD, febuxostat 120 mg QD, febuxostat 240 mg

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QD, and allopurinol 300/100 mg QD treatment groups (226.1, 228.9, 227.2, and 226.4 pounds, respectively).

Among febuxostat subjects enrolled in the Phase 2/3 studies, the majority were male (95%) and most were Caucasian (79%). Subjects ranged in age from 22 to 84 years, with a mean age of 51.8 years. The mean BMI for all febuxostat subjects was 32.7 kg/m² and 63% had a BMI of ≥ 30 kg/m².

Among allopurinol 300/100 mg QD subjects enrolled in the Phase 2/3 studies, the majority were male (95%) and most were Caucasian (76%). Subjects ranged in age from 24 to 84 years, with a mean age of 51.5 years. The mean BMI for all allopurinol 300/100 mg QD subjects was 32.8 kg/m² and 61% had a BMI of ≥ 30 kg/m².

Among placebo subjects enrolled in the Phase 2/3 studies, the majority were male (90%) and most were Caucasian (81%). Subjects ranged in age from 26 to 82 years, with a mean age of 51.7 years. The mean BMI for all placebo subjects was 31.9 kg/m² and 55% had a BMI of ≥ 30 kg/m². (Table 52)

Table 52 (Sponsor's Table 2.4a, ISS)
Demographic and Baseline Characteristics in Phase 2/3 Studies

Variable	Placebo (N=172)	Febuxostat					Allopurinol 300/100 mg QD (N=623)
		All Doses (N=1707)	40 mg QD (N=46)	80 mg QD (N=1180)	120 mg QD (N=876)	240 mg QD (N=134)	
Gender							
Female	17 (10%)	90 (5%)	4 (9%)	61 (5%)	42 (5%)	8 (6%)	32 (5%)
Male	155 (90%)	1617 (95%)	42 (91%)	1119 (95%)	834 (95%)	126 (94%)	597 (95%)
Race							
Caucasian	140 (81%)	1353 (79%)	40 (87%)	932 (79%)	701 (80%)	167 (80%)	480 (76%)
Black	12 (7%)	183 (10%)	4 (9%)	116 (10%)	78 (9%)	13 (10%)	63 (10%)
Hispanic	11 (6%)	100 (6%)	1 (2%)	68 (6%)	52 (6%)	8 (6%)	45 (7%)
Asian	5 (3%)	43 (3%)	0	31 (3%)	22 (3%)	1 (1%)	16 (3%)
Other	6 (3%)	48 (3%)	1 (2%)	33 (3%)	23 (3%)	5 (4%)	25 (4%)
Age (years)^a							
<45	48 (28%)	494 (29%)	10 (22%)	348 (30%)	267 (30%)	33 (25%)	199 (32%)
45 to 65	101 (59%)	974 (57%)	26 (57%)	673 (57%)	501 (57%)	77 (57%)	349 (56%)
>65	23 (13%)	239 (14%)	10 (22%)	159 (14%)	108 (12%)	24 (18%)	81 (13%)
Mean (SD)	51.7 (12.25)	51.8 (12.16)	52.4 (13.38)	51.5 (11.93)	51.1 (11.97)	54.3 (12.83)	51.5 (12.21)
Range	26-82	22-84	23-80	22-84	23-81	30-82	24-84
Weight (pounds)^a							
Mean (SD)	216.5 (41.22)	225.9 (44.85)	218.2 (31.43)	226.1 (43.86)	228.9 (46.68)	227.2 (49.04)	226.4 (45.83)
Range	123-360	123-468	170-277	123-425	136-468	139-425	136-488
Height (inches)^a							
N	172	1701	46	1180	873	131	623
Mean (SD)	69.2 (3.68)	69.7 (3.23)	70.0 (3.42)	69.8 (3.25)	69.8 (3.17)	69.7 (3.38)	69.6 (3.36)
Range	47-76	59-83	62-80	59-80	59-82	61-83	59-79
BMI (kg/m²)^a							
N	172	1701	46	1180	873	131	623
18.5 to <25	16 (9%)	87 (5%)	3 (7%)	61 (5%)	38 (4%)	9 (7%)	27 (4%)
25 to <30	61 (35%)	545 (32%)	16 (35%)	370 (31%)	274 (31%)	42 (31%)	214 (34%)
≥ 30	95 (55%)	1072 (63%)	27 (59%)	749 (63%)	561 (64%)	83 (62%)	384 (61%)
Mean (SD)	31.9 (6.01)	32.7 (6.03)	31.4 (4.53)	32.6 (5.95)	32.9 (6.09)	32.8 (6.53)	32.8 (6.21)
Range	21.8-53.2	20.3-64.6	24.1-42.6	20.3-64.6	20.7-63.5	21.0-64.6	19.6-64.6

SD = standard deviation

Phase 2/3 studies included: TMX-00-004, TMX-01-005, C02-009, C02-010, and C02-021.

a At baseline.

Cross-reference: Statistical Table 2.3.2

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