Febuxostat 40 mg and 80 mg

NDA No. 21-856

Indication: Treatment of hyperuricemia in patients with gout

Briefing Document for Advisory Committee

Division of Anesthesia, Analgesia, and Rheumatology Products

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Takeda Pharmaceuticals North America, Inc
One Takeda Parkway
Deerfield, IL 60015

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List of Abbreviations and Definitions of Terms

AAC	Arthritis Advisory Committee
ACE	angiotensin-converting enzyme
AE	adverse event
AHS	allopurinol hypersensitivity syndrome
ALT	alanine aminotransferase
APEX	Study C02-009 (**A**llopurinol and **P**lacebo **E**valuation of Febu**X**ostat)
APTC	Anti-Platelet Trialists' Collaboration
ARA	American Rheumatism Association
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
A-V	atrioventricular
BID	twice daily
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CHF	congestive heart failure
CI	confidence interval
C_{max}	maximum plasma concentration
CrCl	creatinine clearance
CL/F	apparent total body clearance
CMH	Cochrane-Mantel-Haenszel
CONFIRMS	Study F-GT06-153 (**Con**firmation of **F**ebuxostat **i**n **R**educing and **M**aintaining **S**erum Urate)
COX-2	cyclooxygenase-2
CV	cardiovascular
CYP	cytochrome P450
DBP	diastolic blood pressure
DDI	drug-drug interaction
ECG	electrocardiogram
EULAR	European League Against Rheumatism
EXCEL	Study C02-021 (F**e**bu**x**ostat/Allopurinol **C**omparative **E**xtension **L**ong-Term Study)
FACT	Study C02-010 (**F**ebuxostat and **A**llopurinol **C**ontrolled **T**rial)
FDA	Food and Drug Administration
FOCUS	Study TMX-01-005 (**F**ebuxostat **O**pen-Label **C**linical Trial of **U**rate-Lowering **S**afety and Efficacy)

GI	gastrointestinal
hERG	human ether à go-go-related gene
HGPRT	hypoxanthine-guanine phosphoribosyltransferase
HLT	High Level Term (MedDRA Classification)
IBW	ideal body weight
INR	international normalization ratio (for anticoagulation monitoring)
ITT	intent to treat
LFT	liver function test
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MSU	monosodium urate
NA	not applicable
N/A	not available
NDA	New Drug Application
NE	treatment/dose not evaluated
NEC	not elsewhere classified
NHANES	National Health and Nutrition Examination Surveys
NSAID	nonsteroidal anti-inflammatory drug
OMPDC	orotidine-monophosphate decarboxylase
OPRT	orotate phosphoribosyltransferase
PCI	potentially clinically important
PD	pharmacodynamics
PK	pharmacokinetics
PNP	purine nucleoside phosphorylase
PReCIS	Preventive Cardiology Information System Database Cohort Study
PRPP	phosphoribosyle pyrophosphate
PT	Preferred Term (MedDRA Classification)
PY	patient-years of exposure
QD	once daily
QTcF	Fridericia-corrected QT interval
RCT	randomized controlled trial
SAE	serious adverse event
SBP	systolic blood pressure
sUA	serum urate
T_3	triiodothyronine
T_4	levothyroxine
Takeda	Takeda Pharmaceuticals North America, Inc

TEN	toxic epidermal necrolysis
t_{max}	time to maximum drug concentration
TMX-67	drug code used prior to attributing generic name, febuxostat
TSH	thyroid-stimulating hormone
UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit of normal
ULT	urate-lowering therapy
URAT1	urate-anion transporter
URTI	upper respiratory tract infection
USA	United States of America
V_{ss}/F	apparent volume of distribution at steady state
XO	xanthine oxidase

1 Executive Summary

1.1 Overview

This document has been prepared for the Arthritis Advisory Committee (AAC) of the Food and Drug Administration (FDA) for the meeting scheduled on 24 November 2008. During this meeting the committee will discuss febuxostat, a nonpurine selective inhibitor of xanthine oxidase (XO), for the following indication: *treatment of hyperuricemia in patients with gout*.

1.2 Disease Background

Gout affects 3 to 5 million individuals in the United States (USA) and is increasing in incidence and prevalence.[1-4] Gout is a serious health condition characterized by flares of acute arthritis, chronic gouty arthropathy, tophi, and uric acid urolithiasis, and is associated with a broad range of comorbidities, including cardiovascular disease, chronic kidney disease, and metabolic syndrome.[5-7] The underlying metabolic aberration in gout is hyperuricemia, which is defined as an elevation in serum urate (sUA) level ≥6.8 mg/dL. Hyperuricemia develops into gout when urate crystals are formed from supersaturated body fluids and deposited in joints, tophi, and parenchymal organs.

1.3 Treatment and Unmet Medical Need

Urate-lowering therapy (ULT) is used to treat hyperuricemia in patients with gout. The goal of therapy is to reduce sUA to 6.0 mg/dL or less, below the concentration at which monosodium urate saturates extracellular fluid.[8] Using ULT to reduce and maintain sUA levels <6.0 mg/dL ultimately improves the clinical symptoms of gout by reducing the frequency of gout flares, decreasing size and number of tophi, and improving quality of life.[9-11] Due to the potential for paradoxical flares caused by urate crystal mobilization, anti-inflammatory agents and/or colchicine are given as prophylaxis with ULT during the first months of treatment.

Currently available ULTs work in 2 ways. Uricosuric agents increase renal uric acid excretion, and XO inhibitors decrease uric acid production. The most commonly prescribed ULT in the USA is allopurinol, a purine analogue and nonselective XO inhibitor. Oxypurinol, the active metabolite of allopurinol is renally excreted, and allopurinol requires dose reduction in patients

with renal impairment. Although approved in 1966 for use at doses ranging from 100 mg to 800 mg daily, allopurinol is commonly dosed at 100 mg to 300 mg daily, with 95% of prescriptions being written for 300 mg or less.[12] Recent studies, however, show that less than 50% of gout patients achieve sUA levels <6.0 mg/dL with the 300 mg dose.[13-15] Higher doses of allopurinol (>300 mg/day) have not been widely used out of concern for adverse drug reactions, especially rashes (in approximately 2-5% of patients) and, in particular, a rare, but frequently fatal, allopurinol hypersensitivity syndrome.[16]

Due to the limitation of the available ULT options, clinicians need a more potent and tolerable agent that is efficacious in treating all patients with gout, but especially patients with renal impairment, with higher sUA levels, and with tophi whose needs are poorly met by existing medications.

1.4 Mechanism of Action

Febuxostat is a potent, nonpurine, selective inhibitor of XO that exhibits antihyperuricemic activity by reducing the formation of uric acid. Uric acid is the end product of purine metabolism and is generated in the cascade of hypoxanthine →xanthine →uric acid. Both steps in this transformation are catalyzed by XO. Febuxostat has been shown to potently inhibit both the oxidized and reduced forms of XO.[17] Unlike febuxostat, administration of allopurinol does not provide persistent enzyme inhibition and has weaker hypouricemic activity. More importantly, because allopurinol and its metabolites are purine analogs, they also inhibit other enzymes involved in purine and pyrimidine metabolism. In contrast, febuxostat is a selective inhibitor of XO.[18]

1.5 Nonclinical Pharmacology and Toxicology

A comprehensive pharmacological and toxicological evaluation of febuxostat was conducted to either meet or exceed the nonclinical safety requirement as per regulatory guidelines for chronic use of human drugs. In addition, pharmacology studies demonstrated no mechanisms associated with febuxostat that would lead to unwanted cardiovascular (CV) effects at therapeutic doses. In animal models specific for CV disorders, febuxostat had no detrimental CV effect, but rather appeared to have beneficial CV effects.

1.6 Clinical Pharmacology

The clinical pharmacology of febuxostat has been characterized in 25 Phase 1 studies in healthy subjects and confirmed in subjects with gout by population pharmacokinetic data from two Phase 2 and 3 clinical studies. Key findings include the following:

- Febuxostat is rapidly (t_{max} 1.0-1.8 h) and extensively absorbed (>80%) following oral administration, and no appreciable accumulation of febuxostat was found following multiple once-daily (QD) dosing.
- Febuxostat is almost entirely eliminated by liver metabolism, with <4% of orally administered febuxostat being eliminated in the urine as unchanged drug. Therefore, renal impairment does not have a major impact on the elimination of febuxostat from the plasma. This is in contrast to oxypurinol, which is eliminated almost entirely by the kidneys.
- Febuxostat effectively decreases sUA in both healthy subjects and in subjects with hyperuricemia and gout. The maximum pharmacodynamic effect (decrease in sUA) is reached within one week of daily dosing.
- No clinically relevant gender or age differences were observed in the pharmacokinetics or pharmacodynamics of febuxostat. Similarly, the percent decrease in sUA between normal subjects and subjects with mild or moderate hepatic or renal impairment did not differ. No dose adjustment of febuxostat is needed in these patient groups.
- Febuxostat in doses up to 300 mg QD, at steady state, did not cause prolongation of the QTc interval in healthy subjects in a QTc safety study.

1.7 Clinical Development Program

Febuxostat has been studied for the treatment of hyperuricemia in subjects with gout. A New Drug Application (NDA) for febuxostat was first submitted for the recommended febuxostat doses of 80 mg and 120 mg. That recommendation was based on data from one Phase 2 placebo-controlled, dose-ranging study, two active-controlled Phase 3 studies, and interim data

from two open-label, long-term extension studies. Following the initial application, the FDA requested that the safety profile be examined further due to an imbalance in the number of cardiovascular/thrombotic adverse events reported for febuxostat compared to allopurinol or placebo. TAP Pharmaceutical Products, Inc (now part of Takeda Pharmaceuticals of North America, Inc [Takeda]) submitted results of an independent adjudication of the CV events reported in the Phase 2 and 3 and long-term studies, along with interim results from the ongoing long-term studies.

The FDA subsequently requested additional clinical data to more clearly characterize the potential CV risks of febuxostat 80 mg and to evaluate a lower dose of febuxostat. Based on discussions with FDA, a new, large (N=2269) Phase 3 controlled study (CONFIRMS) was conducted comparing febuxostat 40 mg and 80 mg with allopurinol. This study included a prospective adjudication of CV adverse events by an independent committee, based on the Anti-Platelet Trialists' Collaborations (APTC) criteria[19] modified by White, et al.[20]

Results from the CONFIRMS Study supported the efficacy observed with febuxostat 40 mg in the Phase 2 dose-ranging study and the safety of febuxostat 80 mg. Based on the demonstrated efficacy of the 40 mg and 80 mg doses, Takeda is no longer pursuing the 120 mg dose for approval. Approval is requested for marketing the febuxostat 40 mg and 80 mg doses for the treatment of hyperuricemia in patients with gout.

1.8 Clinical Efficacy

The efficacy of febuxostat was evaluated in one placebo-controlled dose-ranging study (Dose-Ranging Study), one Phase 3, placebo- and active-controlled study (28-week APEX Study), and two Phase 3, active-controlled studies (52-week FACT Study and 6-month CONFIRMS Study). Long-term (up to 5 years) efficacy was evaluated in two open-label extension studies (FOCUS and EXCEL). The study designs are described in Section 6.2.

Total enrollment in these Phase 2 and 3 studies included 4254 subjects with hyperuricemia and gout. Inclusion criteria were similar for all four studies and required that subjects have baseline sUA ≥8.0 mg/dL and a diagnosis of gout. Exclusion criteria were similar across the controlled

studies and included secondary hyperuricemia, severe renal impairment, active liver disease, or clinical instability due to a significant medical condition.

All studies demonstrate the efficacy of febuxostat based on the protocol-specified primary endpoint. The primary endpoint differed slightly across studies (sUA levels at last 3 measurements in the APEX and FACT Studies; sUA levels at the Final Visit in the Dose-Ranging and CONFIRMS Studies). For comparison of efficacy across studies, the response rates based on sUA at the Final Visit are shown in Table 1.

Table 1 Proportion of Subjects With sUA Levels <6.0 mg/dL at the Final Visit

Study	Placebo	Febuxostat 40 mg	Febuxostat 80 mg	Allopurinol
Phase 2 Dose-Ranging	0% (0/35)	56%[e] (19/34)	76%[e] (28/37)	NE
APEX[a]	1% (1/127)	NE	72%[b,e] (183/253)	39%[e] (102/263)
FACT[a]	NE	NE	74%[b] (185/249)	36% (88/242)
CONFIRMS	NE	45%[d] (342/757)	67%[b,c] (507/756)	42% (318/755)

NE = treatment/dose not evaluated.

a Primary endpoint was sUA level at last 3 measurements; sUA at Final Visit was a secondary endpoint. The results of treatment comparisons for the endpoint of the Final Visit were consistent with those obtained for the endpoint of the last 3 sUA levels.

b Indicates statistical significance versus allopurinol at $p<0.001$.

c Indicates statistical significance versus febuxostat 40 mg at $p<0.001$.

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

e Indicates statistical significance versus placebo at $p<0.001$.

Febuxostat 40 mg is more efficacious than placebo and similar to allopurinol in the ability to lower and maintain sUA <6.0 mg/dL. Febuxostat 80 mg is superior to allopurinol and febuxostat 40 mg in the ability to lower and maintain sUA <6.0 mg/dL.

Febuxostat was effective in a range of subgroups of subjects based on data from the large CONFIRMS Study (Table 2). Febuxostat 80 mg is superior to allopurinol and febuxostat 40 mg in subjects with baseline tophi or sUA levels ≥10.0 mg/dL, while both febuxostat 40 mg and 80 mg have enhanced efficacy compared to allopurinol in subjects with mild or moderate renal impairment.

Table 2 Proportion of Subjects With sUA <6.0 mg/dL by Subgroups (CONFIRMS)

Baseline Status	Febuxostat 40 mg		Febuxostat 80 mg		Allopurinol	
	N	%	N	%	N	%
sUA ≥10 mg/mL	249	27	254	49[b]	230	31
Tophi	166	35	163	57[b]	148	32
Mild/Moderate Renal Impairment[a]	479	50[c]	503	72[b]	501	42

a Mild and moderate renal impairment was defined using estimated creatinine clearance (CrCl) at baseline, calculated using the Cockcroft-Gault formula corrected for ideal body weight. Mild impairment: CrCl = 60-89 mL/min; moderate impairment: CrCl = 30-59 mL/min.
b Febuxostat 80 mg was superior ($p<0.001$) to both febuxostat 40 mg and allopurinol.
c Statistically significant difference ($p<0.05$) between febuxostat 40 mg dose and allopurinol.

Long-term use of febuxostat was shown to effectively maintain sUA levels <6.0 mg/dL, leading to fewer gout flares and resolution of tophi. In the FOCUS Study, the percentages of subjects who experienced gout flares dropped from 39% during the first 6 months to <10% after approximately 24 months, <4% after approximately 48 months, and to almost zero at the end of the study. The EXCEL Study included subjects with up to 40 months of exposure, and similar to the FOCUS Study, gout flares dropped from 30% during the first 6 months to <10% after approximately 24 months, and to almost zero at the end of the study. Resolution of the primary palpable tophus occurred in 69% of subjects with tophi in the FOCUS Study and 42% in the EXCEL Study.

1.9 Clinical Safety

Febuxostat was well-tolerated in the clinical studies, which enrolled subjects representative of the hyperuricemic gout population. The development program for febuxostat included 4072 subjects who received at least one dose of febuxostat, with doses ranging from 10 mg to 300 mg. Of those, 2757 subjects received febuxostat 40 mg or 80 mg in Phase 2 and Phase 3 studies.

Febuxostat has a well-characterized safety profile, which is based on the following data:

- The incidence of treatment-emergent adverse events (AEs) in the Phase 3 controlled studies (APEX, FACT, and CONFIRMS) were comparable in the febuxostat 40 mg (57%), febuxostat 80 mg (62%), and allopurinol (66%) groups. The most frequent AEs

across treatment groups were upper respiratory tract infections (URTI), musculoskeletal and connective tissue signs and symptoms, and diarrhea.

- Febuxostat was well-tolerated during long-term treatment (up to 5 years). The incidence of AEs did not increase over time, and no new type of AE emerged with long-term use. The most frequently reported AE in all treatment groups was URTI.
- Deaths occurred at similar rates in febuxostat- and allopurinol-treated subjects in the Phase 3 controlled studies (0.22% and 0.23%). Ten deaths occurred during the open-label, long-term studies for a rate of 0.38 deaths/100 patient-years of exposure (PY), which was similar to the rate of 0.45 deaths/100 PY for febuxostat during the Phase 3 controlled studies. There was no discernible pattern with respect to treatment duration or time of death.
- The rates of CV events were low across treatment groups. There were no clinically significant differences in the CV AEs in febuxostat- compared to allopurinol-treated subjects. CV events and deaths were adjudicated using the predefined endpoints specified by the APTC.[19,20] Events were adjudicated as APTC events (CV deaths, nonfatal myocardial infarctions, and nonfatal strokes) and non-APTC CV events (included angina, coronary revascularization, transient ischemic attack, cerebral revascularization, arterial vascular thrombotic events, nonfatal congestive heart failure, and arrhythmia).
    - In the CONFIRMS study, which was designed to prospectively evaluate CV events, no APTC events were observed in the 40 mg group. The febuxostat 80 mg and allopurinol groups had the same rate (0.4%) of APTC events.
    - In the combined Phase 3 controlled studies, adjudicated APTC events were experienced by a small number of subjects across treatment groups. The rate of APTC events was 0%, 0.55%, and 0.31% in the febuxostat 40 mg, febuxostat 80 mg, and allopurinol groups. For all febuxostat-treated subjects combined, the incidence rate of APTC events was 0.37%.

- Non-APTC CV events in the combined Phase 3 controlled studies occurred in similar rates across the febuxostat 40 mg, febuxostat 80 mg, and allopurinol groups.
- In the long-term extension studies, the rates of adjudicated APTC and non-APTC CV events were low and did not increase over time.

- Hepatic transaminase elevations with febuxostat were generally mild and both the incidence and severity were similar to those observed with allopurinol. No Hy's Law or serious drug-induced liver injury occurred during the studies.
- A Phase 1 study demonstrated that a dose adjustment is not necessary for patients with mild or moderate renal impairment. The controlled studies did not have dose adjustments with febuxostat for subjects with renal impairment and in those subjects febuxostat was well tolerated.
- The majority of dermatologic events were mild to moderate in severity and not considered related to study drug. Febuxostat-treated subjects did not experience any life-threatening, serious cutaneous adverse reaction, such as Stevens-Johnson Syndrome or toxic epidermal necrolysis (TEN). One allopurinol-treated subject experienced a serious episode identified as allopurinol hypersensitivity syndrome (AHS).

1.10 Dose Recommendations

Based on the optimal risk-benefit balance, febuxostat 40 mg and 80 mg doses are both recommended for approval to allow clinicians individualized dosing options. The 80 mg dose is more effective in subjects with more severe disease as defined by the presence of tophi or higher sUA levels. The efficacy of both doses in reducing sUA levels to <6.0 mg/dL has been shown to be reproducible in randomized, controlled studies.

1.11 Postmarketing Commitments

Once febuxostat is approved for marketing, Takeda has committed to continue investigating the association between reduction of sUA levels and reduction in gout flares over time. A Phase 4, randomized study has been designed to compare febuxostat to allopurinol for the reduction of

gout flares. In addition, XO inhibitors have been reported to increase concentrations of theophylline, so Takeda has agreed to conduct a postmarketing Phase 1 drug-drug interaction study of the effect of multiple doses of febuxostat on the pharmacokinetics of theophylline.

1.12 Benefit and Risks of Febuxostat

1.12.1 Unmet Medical Need

Gout is a progressive and debilitating disease associated with multiple comorbid conditions. Gout is caused by deposition of urate crystals in joints and parenchymal organs and the clinical manifestations, such as flares and tophi, are a direct result from these crystals. Management of gout and prevention of flares and tophi resolution are accomplished by maintaining sUA <6.0 mg/dL.

Current treatment options are limited. The most commonly prescribed therapy is allopurinol, which is a purine XO inhibitor that lacks enzyme specificity. Allopurinol is typically used at 300 mg QD, with a lower dose recommended for patients with renal impairment. Recent studies have shown that less than half of gout patients treated with allopurinol (typically 300 mg) achieve the level of sUA needed for effective management of the disease. Other limitations (drug interactions) or safety concerns (hypersensitivity reactions) also limit the utility of allopurinol. Allopurinol has a long history of use, but had not been studied rigorously in adequate and well-controlled studies. In addition, there are limited data from controlled clinical studies available to support higher dosing for allopurinol. When weighing the benefits and risks of therapeutic options, it is important to consider all relevant information. This required careful consideration not only of the product under review, but also of the potential alternative treatments.

The febuxostat clinical program thoroughly studied more than 4000 subjects and demonstrates that febuxostat provides clear benefits for patients with hyperuricemia and gout. The development program included subjects representative of the general gout population who have a wide range of comorbid conditions (eg, multiple CV risk factors, renal impairment, obesity, diabetes, and hyperlipidemia).

1.12.2 Benefits of Febuxostat

Reduction of sUA

Febuxostat has been proven effective in lowering and maintaining sUA <6.0 mg/dL. Achieving and maintaining a sUA level of <6.0 mg/dL is accompanied by reduction in gout flares and resolution of tophi, the clinical manifestations of gout. Febuxostat 40 mg has similar effectiveness in reduction of sUA as allopurinol.

Febuxostat 80 mg had statistically significantly greater proportions of subjects with sUA<6.0 mg/dL at the final study visit than the allopurinol group in all Phase 3 randomized controlled studies. This difference in the absolute rate ranging from 25%-38% for febuxostat 80 mg over allopurinol clearly establishes the added benefit of febuxostat 80 mg compared to allopurinol. Febuxostat 80 mg also demonstrates a therapeutic advantage over febuxostat 40 mg (20%-22% absolute difference in response rates). In addition, febuxostat 80 mg was effective in subjects with more severe disease, such as higher sUA levels or the presence of tophi.

Treatment Option for Patients with Comorbid Conditions

A high percentage of gout patients have some degree of renal impairment. Febuxostat 40 mg and 80 mg were effective in subjects with mild-to-moderate renal impairment. The safety profile among subjects with moderate renal impairment was similar to those for subjects with normal or mildly impaired renal function. As a result, there is no dose adjustment required with febuxostat. This is in contrast to allopurinol, which requires dose reduction to decrease potential adverse events in patients with renal impairment.

Patients with gout have multiple comorbidities requiring a range of medications raising concerns related to drug-drug interactions. Febuxostat has shown no significant drug interactions with commonly used drugs and can safely be administered concurrently with a wide variety of drugs.

Lack of Severe Skin Reactions

No serious skin reactions occurred in febuxostat-treated subjects. There was no hypersensitivity reaction associated with febuxostat. Allopurinol is known to have very serious skin reactions

(AHS) with potentially fatal outcomes. One case of AHS in a subject on allopurinol was reported in the febuxostat clinical program.

1.12.3 Potential Risks of Febuxostat

Cardiovascular Safety

A thorough evaluation of a potential CV risk was undertaken. These steps included a detailed review of CV (APTC) endpoints in the APEX and FACT Studies. In these two initial Phase 3 studies, APTC events were numerically low, but there was an imbalance in the rate of events for febuxostat 80 mg and 120 mg compared to allopurinol or placebo. For both studies, the APTC evaluation process was done as part of a safety review after the studies were completed. To address this issue more fully, a new randomized, controlled study (CONFIRMS) was developed in which CV endpoint determination was defined prospectively.

The numerical imbalance was not seen in this larger Phase 3 study. In the CONFIRMS Study, there was no evidence of CV risk for febuxostat 40 mg; the incidence rates of adjudicated APTC events were low and similar for febuxostat 80 mg and allopurinol. No mechanism that would associate febuxostat with detrimental CV effects in humans was observed in nonclinical studies. In addition, febuxostat showed no untoward effect on blood pressure in our clinical studies.

Hepatic Effects

Hepatic effects were generally mild and the percentage of subjects with transaminase elevations ≥3 xULN was low and similar for febuxostat- and allopurinol-treated subjects. No dose response was seen across febuxostat treatment groups. However, as with allopurinol, periodic liver function tests are recommended during therapy.

Treatment-Initiated Gout Flares

Paradoxical gout flares are an unavoidable consequence of urate-lowering therapy. The greater the magnitude of the reduction of sUA, the greater the incidence of gout flare. Therefore, more potent agents are associated with more treatment-initiated flares. It is recommended that with initiation of any ULT, such as febuxostat, patients should receive concomitant prophylaxis (eg, colchicine or nonsteroidal anti-inflammatory drugs [NSAIDs]) for gout flares.

1.13 Summary and Conclusions

Febuxostat is a potent, nonpurine, selective inhibitor of XO, which has been shown to be effective in reducing and maintaining sUA <6.0 mg/dL at doses of 40 mg and 80 mg. Maintaining these sUA levels is associated with the clinical benefits of tophi resolution and reduction in gout flare. Febuxostat 40 mg and 80 mg provide an effective treatment option for patients with hyperuricemia and gout. Based on the clinical data, 40 mg and 80 mg are effective doses with 80 mg providing added benefit for patients with more severe disease. Febuxostat also provides benefit in this patient population with comorbid conditions and has an advantage over allopurinol of not requiring dose adjustment in patients with mild to moderate renal impairment. Febuxostat doses of 40 mg and 80 mg are well tolerated and have a similar safety profile as the currently marketed allopurinol. The rates of CV events observed in the febuxostat clinical program were low. The potential CV risk was prospectively evaluated in the CONFIRMS Study and no difference in the rate of CV events was observed between febuxostat 80 mg and allopurinol; whereas, with its known risk of AHS, the risk in terms of severe rash is greater with allopurinol.

Febuxostat 40 mg and 80 mg doses are both recommended for approval to allow clinicians individualized dosing options. The 80 mg dose is more effective than 40 mg, especially in subjects with more severe disease as defined by the presence of tophi or higher sUA levels. Overall, the benefits of febuxostat 40 mg and 80 mg clearly outweigh the risks and support approval of febuxostat for the treatment of hyperuricemia in patients with gout.

2 Background

Gout is a serious health condition characterized by flares of acute arthritis, chronic gouty arthropathy, tophi, and uric acid urolithiasis and associated with a broad range of comorbidities including cardiovascular disease, chronic kidney disease, and metabolic syndrome. Gout can be successfully managed by reducing and maintaining sUA levels <6.0 mg/dL.[21] Medications are the mainstay of current urate-lowering therapy (ULT). Available therapies have limitations, particularly in patients with renal impairment and/or with more advanced/severe disease. Additional well-studied treatment options are needed for patients with hyperuricemia and gout.

2.1 Hyperuricemia

Hyperuricemia is defined as sUA >6.8 mg/dL, the limit of solubility of urate in extracellular fluids.[22] Urate is the end product of purine metabolism, and is produced by sequential oxidation of hypoxanthine to xanthine and xanthine to uric acid. Both reactions are catalyzed by the enzyme XO.[23] Hyperuricemia may result from increased urate production from either endogenous or exogenous sources, from decreased renal uric acid excretion due to deficits in renal uric acid clearance, or from a combination of these 2 mechanisms, with the majority from impaired renal acid clearance.[24]

2.2 Clinical Effects of Hyperuricemia

Hyperuricemia is one of the biochemical and clinical hallmarks of gout, but is also associated with a range of other disease states, such as cardiovascular disease, kidney disease, and metabolic dysfunctions.[25-27]

2.2.1 Gout

Hyperuricemia develops into gout when urate crystals are formed from supersaturated body fluids and deposited in gouty joints, tophi, and parenchymal organs. Uric acid crystals may also form as stones in the renal collecting systems and urinary tract.

Gout is a common and increasingly significant cause of acute and chronic disability and impaired quality of life. The prevalence of gout in the USA is estimate to range from 3 to 5 million

individuals. Prevalence increases with age and is higher in men than in women at all ages and gout the most common arthritis in men.[26,28]

Gout incidence is expected to continue to increase due to an aging population, increasing obesity, and increasing incidence of metabolic syndrome.[1] Both the advancing age and frequent comorbidities of the gouty population contribute to the suboptimal patient outcomes of current gout management.[2]

Gout is a progressive disease with a relatively predictable course. The first event is usually an attack of intensely painful and acutely disabling inflammatory arthritis that typically lasts ≤10 days without treatment. Initial attacks usually involve a single joint in the lower extremity, especially at the base of the great toe, ankle, or knee. Subsequent acute attacks are common, occurring in more than 70% of patients within 2 years and more than 90% within 5 years.[29] The pain and disability during an acute gouty flare are accompanied by swelling, redness, and tenderness and synovial effusion containing abundant neutrophils (acute inflammatory cells), many of which contain ingested urate crystals.[30]

In the intervals between acute attacks, deposited crystals and low-grade inflammatory cell infiltrates are retained in the synovium and synovial fluid of previously involved joints.[31] Thus, low-grade urate crystal-induced inflammation is an on-going process. Lowering urate to sub-saturating levels should deplete the crystals and result in clinical benefit by decreasing urate crystal chemotaxis for inflammatory cells. Large multiple masses of urate crystals embedded in a low-grade chronic inflammatory cell infiltrate are called tophi. Tophi are locally destructive lesions that cause joint deformities, bony erosion, cartilage disruption, and peripheral nerve compression syndromes. Skin and subcutaneous tissue involvement can result in chronic ulceration and infection.

Tophi are often accompanied by increasingly chronic disability and progressively compromised quality of life. Approximately 20% of patients with gout have tophi,[24] and patients in the stage of chronic tophaceous gout are often disabled and have substantially diminished health-related quality of life.[9,32] Lowering and maintaining sUA levels at <6.0 mg/dL has been shown to result

in resolution of tophi.[33] Tophi resolution with allopurinol treatment has been reported to take as long as 2 years when sUA is maintained at <6.0 mg/dL.[10] Recent reports confirm that the lower the sUA level , the faster tophi will resolve.[10,33]

2.2.2 Comorbid Conditions

Gout patients have an inordinately high incidence of comorbidities that may be associated with hyperuricemia or gout or both conditions. Patients with gout not only suffer potentially disabling and deforming arthritic disease, but are also at a high risk for cardiovascular and metabolic disorders that may be associated with disordered urate metabolism.

There is a growing body of literature demonstrating that sUA level is an independent predictive factor for cardiovascular disease when the effect of other risk factors have been controlled.[25,26] Epidemiological data clearly implicate hyperuricemia as a risk factor in many of these comorbid states.[27] Several recent studies report an increased risk of CV death, myocardial infarction, and stroke associated with higher sUA levels (see Appendix 1 for a list of studies). For example, the Preventive Cardiology Information System Database Cohort Study (PReCIS), which assessed the prognostic value of sUA in 3098 persons (ages 18 to 87 years) at risk for cardiovascular disease, found that sUA was an independent predictor of cardiovascular death. This study found a 39% increase in the risk of cardiovascular death for each 1 mg/dL increase in sUA level (hazard ratio: 1.26; $p \leq 0.001$).[34]

The Framingham study results showed that sUA was not an independent predictor of coronary artery disease in men without gout, however, there was a 60% excess incidence of coronary artery disease in gouty men never treated with diuretics.[35] A National Health and Nutrition Examination Surveys (NHANES) study reported a direct role for hyperuricemia in cardiovascular events and mortality, tying sUA levels to increasing cardiovascular mortality. These findings persisted even after adjustments were made for age, sex, race, body mass index (BMI), smoking, hypertension, and diabetes.[36] There is increasing evidence that high sUA levels are an independent CV risk factor.

2.3 Current Management of Hyperuricemia

Antihyperuricemic drugs provide a definitive method for controlling hyperuricemia in patients with gout. It is the long-term control of hyperuricemia that ultimately results in improvement in the clinical symptoms of gout. In general, the aim of therapy is to reduce sUA to 6.0 mg/dL or less, below the concentration at which monosodium urate saturates extracellular fluid.[23] This reduction and maintenance of sUA levels in a subsaturating range (<6.0 mg/dL, European League Against Rheumatism [EULAR] guidelines)[21] over extended periods of time have been proven to lead to favorable clinical outcomes in gout. These outcomes include reductions in the following key measures: incidence of acute gout flares;[11] numbers of urate crystals in fluid aspirated from gouty joints;[37] size and number of tophi.[10] Further, improvement in patient-reported measures of health-related quality of life and disability has also been reported.[9] The degree of urate reduction determines the rapidity and/or extent to which favorable clinical outcomes can be achieved. For example, rates of tophus resolution are increased as sUA levels are lowered to and maintained at <6.0 mg/dL[10] and rates of gout flare recurrence are substantially less in gouty subjects whose sUA levels are maintained at an average near or below 6.0 mg/dL.[13]

Non-pharmacologic treatment of gout includes dietary restrictions, but even a very restrictive low-purine diet is expected to reduce sUA by only 1 mg/dL.[38,39] Consequently, ULT remains the mainstay of gout management.

Pharmacologic therapies employed currently are grouped into 2 categories: uricosuric agents that promote increased uric acid excretion; and XO inhibitors that decrease uric acid production. Urate-lowering therapy is associated with an increase in the incidence of recurrent gout attacks, and therefore, before discussing the ULT options, the issue of prophylaxis for gout flare is reviewed.

2.3.1 Treatment Initiated Gout Flares and Prophylactic Therapy

Clinically, ULT should be initiated only during the quiescent period between recurrent acute gout attacks. However, even during this clinically silent phase of the disease, ULT has been reported to provoke an acute gout flare in 25% to 75% of patients.[7,40-42]

The precise etiologic mechanism for this response during initiation of ULT is unknown. One common theory is that the rapid lowering of sUA, with more potent drugs, induces a localized precipitation of monosodium urate (MSU) crystals in the cartilage and soft tissue that triggers an acute inflammatory response.[43,44] Another theory is when urate concentrations are lowered, neutrophils are rendered more active with phagocytosis of MSU crystals releasing inflammatory cytokines.[45]

To reduce the risk of paradoxical flares, it is recommended that ULT always be initiated with anti-inflammatory agents (colchicine or NSAIDs). Low-dose colchicine has long been considered the mainstay of acute gout flare prophylaxis although treatment with NSAIDs also reduce the risk for acute gout flare.[46,47] The exact specifications of colchicine treatment (ie, initiation and duration) were not well characterized prior to 2004. In 2004, Borstad and colleagues demonstrated that the mean number of acute gout flares was significantly greater in patients treated with allopurinol alone compared to allopurinol plus colchicine during the first 3 months of treatment (p=0.022), months 3 to 6 (p=0.033), as well as overall (0.008), confirming the benefit of prophylaxis when initiating ULT.[40]

2.3.2 Uricosuric Therapies

Uricosuric drugs increase renal uric acid excretion by reducing net uric acid reabsorption at the proximal renal tubule through inhibition of the activity of the urate-anion transporter, URAT1. Probenecid is a uricosuric agent that was introduced in the 1950s and remains the sole drug of this class available in the USA. Despite demonstrated efficacy, however, probenecid is infrequently used (~5% of ULT prescribed). It is contraindicated in urinary tract stone formers and patients with uric acid overproduction, has a number of drug-drug interactions, and provides limited efficacy in patients with renal function impairment.[48]

2.3.3 Xanthine Oxidase Inhibitors

Allopurinol, a purine analogue and nonselective XO inhibitor, is the most commonly employed ULT in the USA. Oxypurinol, the active metabolite of allopurinol, is renally excreted requiring dose reduction in patients with renal impairment to avoid accumulation. Although approved for use in the USA in a dose range of 100 to 800 mg daily, 90% to 95% of allopurinol prescriptions

are for 100 to 300 mg daily.[12,14,21] This lower dose is common despite evidence showing that less than 50% of current gout patients receiving 300 mg of allopurinol achieve sUA levels <6.0 mg/dL.[13,15]

Higher doses of allopurinol (>300 mg/day) have not been widely employed out of concern for adverse drug reactions, especially rashes (in approximately 2% - 5% of patients) and, in particular, a rare but frequently fatal AHS. This syndrome is characterized by skin reactions, fever, eosinophilia, and multiple-organ involvement with a mortality rate of 25%.[16,49] In addition, allopurinol therapy is associated with gastrointestinal (GI) intolerance, blood cytopenias and abnormal liver function tests.[14,50]

Only one randomized controlled study (allopurinol vs benzbromarone) has evaluated the safety and efficacy of allopurinol at doses greater than 300 mg/day, with 17 subjects receiving 300 mg and 600 mg daily.[51] No studies have evaluated 100 mg or 200 mg doses, the doses commonly used in patients with renal function impairment. Furthermore, there are no clinical trials confirming that dose reduction limits the risks of severe allopurinol toxicity, and downward dose adjustment frequently results in failure to achieve the urate-lowering goal range.[14]

Due to the limitation of the available ULT options, there is a need for an alternative agent in treating all patients with gout, especially patients with renal impairment, patients with higher sUA levels, and patients with tophi.

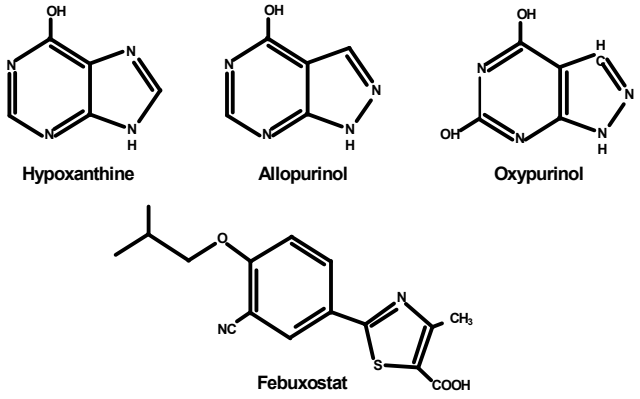
3 Febuxostat Mechanism of Action

Febuxostat is a potent, nonpurine, selective inhibitor of XO that inhibits the formation of uric acid from hypoxanthine and xanthine. The active ingredient in febuxostat immediate release tablets for oral administration is 2-[3-cyano-4-(2-methylpropoxy) phenyl]-4-methylthiazole-5-carboxylic acid. It has a molecular formula of $C_{16}H_{16}N_2O_3S$ and a molecular weight of 316.38.

Uric acid is the end product of purine metabolism in humans and is generated in the cascade of hypoxanthine →xanthine →uric acid. Both steps in this transformation are catalyzed by XO. As a 2-arylthiazole derivative, febuxostat has been shown to potently inhibit both the oxidized and reduced forms of XO by occupying the channel in the enzyme leading to the active sites and

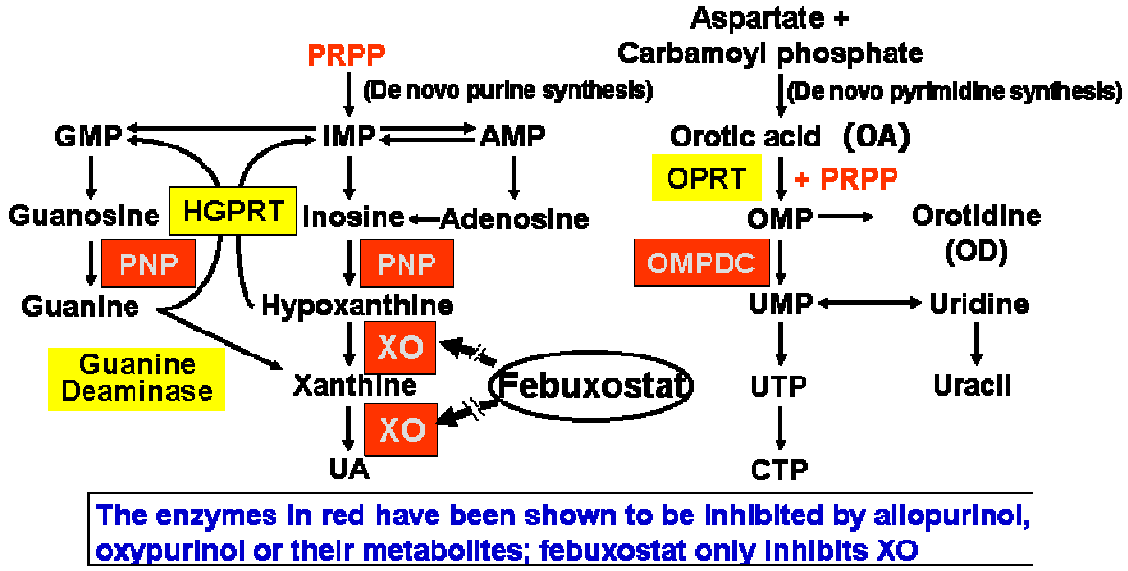
blocking the substrate access to the active sites of the enzyme.[17] In comparison, allopurinol and its active metabolite, oxypurinol, which is formed by oxidation of allopurinol by XO, are both purine analogs (Figure 1). As a substrate of XO, allopurinol is a weak inhibitor of the oxidized form of the enzyme,[52] while oxypurinol only inhibits the reduced form and is released from XO when the enzyme is reoxidized.[53,54] Therefore, unlike febuxostat, administration of allopurinol does not provide persistent enzyme inhibition and has weaker hypouricemic activity.

Figure 1 **Structure of Febuxostat in Comparison to Allopurinol and Oxypurinol**



More importantly, because allopurinol and its metabolites are purine analogs, they can also inhibit other enzymes involved in purine and pyrimidine metabolism (Figure 2). In contrast, febuxostat is a more selective inhibitor of XO.[18]

Figure 2 **Selectivity of Febuxostat on XO in Purine and Pyrimidine Metabolism as Compared to Allopurinol and Its Metabolites (adapted from Takano 2005)**



HGPRT = hypoxanthine-guanine phosphoribosyltransferase; OMPDC = orotidine monophosphate decarboxylase; OPRT = orotate phosphoribosyltransferase; PNP = purine nucleoside phosphorylase; PRPP = phosphoribosylpyrophosphate; XO = xanthine oxidase.

4 Nonclinical Pharmacology and Toxicology

A package of safety pharmacology studies examined the effects of febuxostat on the central nervous, GI, renal, hemostatic, respiratory, and CV (including QT and QTc intervals) systems. High safety margins were found in all studies.

A comprehensive toxicological evaluation of febuxostat was also conducted to either meet or exceed the nonclinical safety requirements as per regulatory guidelines for chronic use of human drugs.

Key findings in relevant organ systems from both pharmacology and toxicology studies are discussed below.

4.1 Cardiovascular Effects

Nonclinical safety pharmacology and secondary pharmacology studies demonstrated no mechanisms associating febuxostat with CV effects at therapeutic doses. Cardiovascular safety pharmacology studies included in vitro electrophysiology investigation on cardiac action potential parameters and ion channels (potassium [hERG], sodium, and calcium), and in vivo studies for hemodynamic and electrocardiogram (ECG) effects in both anesthetized and conscious telemetry dogs. In addition, the in vitro effects of febuxostat on the hemostatic system, protease generation and platelet function were explored using human blood. Febuxostat did not significantly inhibit nor augment platelet or coagulation responses and did not have any interactions in vitro with heparin, warfarin, or aspirin.

Furthermore, in a long-term (52-week) toxicology study in dogs, no CV toxicity was observed based on electrocardiographic, organ weight, and histopathological examinations outside of the kidney (see Section 4.2 for details).

Febuxostat was shown to have no detrimental CV effects in animal CV models:

- In rats with hypertension induced by hyperuricemia, chronic dosing with febuxostat ameliorated systemic and kidney glomerular hypertension and the associated glomerular arteriolar histological changes.[55]
- In rats with fructose-induced metabolic syndrome, chronic treatment with febuxostat after onset of metabolic syndrome significantly lowered fasting triglyceride and insulin levels, and normalized the increased blood pressure.[56]
- In rabbits with myocardial infarction, chronic dosing of febuxostat, initiated shortly after myocardial ischemia, offered significant cardiac functional benefits and delayed or prevented the onset of congestive heart failure (CHF).[57]
- In mice with systolic overload (aortic constriction)-induced CHF, chronic dosing of febuxostat initiated shortly after aortic constriction significantly reduced the cardiac hypertrophy and dysfunction.[58]

- In dogs with rapid pacing-induced CHF, an acute intravenous infusion of febuxostat produced a moderate increase in cardiac contractility and had no effect on the coronary endothelial function and blood flow.[59]
- In dogs, myocardial energetics were measured during basal and high cardiac workout. An acute intravenous infusion of febuxostat produced a favorable bioenergetics effect at both basal and high workout, which suggests that febuxostat has the potential to improve cardiac energy efficiency and dysfunction in CHF.

In summary, when studied in 6 different animal models specific for CV diseases, febuxostat had no detrimental CV effect, but rather appeared to have beneficial CV effects.

4.2 Renal and Urinary Effects

In animals, urinary xanthine excretion with increasing doses of febuxostat can result in the formation of xanthine crystals and calculi due to the exaggerated pharmacological effect of the compound. Irritation by xanthine crystals and calculi led to kidney injury in mice, rats, and dogs, and bladder tumors in mice and rats. However, due to species differences in nucleic acid metabolic turnover, urine volume, urine composition, and urinary tract anatomy, the kidney injury and urinary bladder tumors observed in animals are not expected to occur in humans.[60,61] Xanthine crystal formation was not observed in clinical studies of doses up to 300 mg of febuxostat. Furthermore, in a rat model for chronic renal disease progression, 4-week treatment with febuxostat at a therapeutic dose of 3-4 mg/kg/day did not cause renal damage. Rather, febuxostat treatment ameliorated proteinuria, preserved renal function, and prevented glomerular hypertension. Functional improvement was accompanied by preservation of afferent arteriolar morphology and reduced tubulointerstitial fibrosis.[62]

4.3 Hepatic Effect

Mild hepatic effects (enzyme elevations with no accompanying histological changes in the liver) were observed at high dose levels in rat and dog toxicology studies, where exposure (area under the plasma concentration-time curve [AUC]) levels were much higher (approximately 31-fold or higher) than the mean exposure (AUC) level in humans at the 80 mg dose. In the absence of

histopathological changes indicative of liver injury, enzyme elevations alone in animals following very high exposures to febuxostat were not considered a risk for human exposure.

4.4 Thyroid

Adverse effects related to thyroid (decreases in T_3 and T_4, increases in thyroid-stimulating hormone [TSH] with accompanying follicular cell hyperplasia) were observed at high doses in rats during repeated-dose toxicology studies. Rat thyroid is more sensitive to proliferative lesions caused by chronic TSH stimulation than the human thyroid.[63] Even in rats, the most sensitive species, the effects of febuxostat on the thyroid were observed only at a dose with a 31-fold higher exposure (AUC) compared to the mean exposure (AUC) observed in humans at a dose of 80 mg. Clinical studies revealed no untoward effect on the thyroid, and febuxostat is not expected to be a risk to the thyroid gland in humans.

5 Clinical Pharmacology

5.1 Pharmacokinetics

5.1.1 Absorption

Febuxostat is rapidly and extensively absorbed following oral dose administration, with a t_{max} at approximately 1.0 to 1.8 h and >80% absorbed. There is no accumulation of febuxostat following multiple QD dosing. After single or multiple oral 40 mg and 80 mg QD doses, C_{max} is approximately 1.5 to 1.6 μg/mL and 2.5 to 2.6 μg/mL, respectively. Following a single 40 mg dose or multiple 80 mg QD doses with a high-fat meal, there was a 46% and 49% decrease in C_{max} and a 19% and 18% decrease in AUC, respectively. However, no clinically significant change in the percent decrease in sUA concentration was observed following multiple 80 mg doses. Therefore febuxostat can be taken without regard to food. Concomitant ingestion of an antacid containing magnesium hydroxide and aluminum hydroxide was shown to delay the absorption of febuxostat (approximately 1 h) and to cause a 32% decrease in C_{max}, but no significant change in AUC was observed. Therefore, febuxostat may be taken without regard to antacid use.

5.1.2 Distribution

The apparent steady-state volume of distribution (V_{ss}/F) of febuxostat ranges from 29 to 75 L after oral doses of 10 mg to 300 mg. The plasma-protein binding of febuxostat is approximately 99.2% (primarily to albumin) and is constant over the concentration range achieved with 40 mg and 80 mg doses. There were no differences in the extent of protein binding between young (18-40 years) and elderly (>65 years) subjects, between male and female subjects, or in subjects with varying degrees of hepatic impairment. In subjects with renal impairment, a slight decrease in protein binding of febuxostat with increasing renal impairment was observed (98.8% in subjects with severe renal impairment versus 99.1% in subjects with normal renal function).

5.1.3 Metabolism and Excretion

Following administration of [^{14}C]febuxostat, parent drug accounted for 84% - 96% of plasma total radioactivity profiles through 4 hours postdosing. The half-life of febuxostat in plasma typically ranges from 5 to 8 hours and reaches steady state within one week of once-daily dosing. Metabolites of febuxostat are present in human plasma, but at much lower concentrations compared to parent drug.

Febuxostat is eliminated from the blood mainly by metabolism to glucuronide conjugates in the liver, and to a much lesser degree by oxidative metabolism via cytochrome P450 (CYP450), also in the liver. The glucuronide conjugate of febuxostat formed by several uridine diphosphate glucuronosyltransferase (UGT) isoforms including UGT1A1, UGT1A8, and UGT1A9 is not active and therefore does not contribute to the efficacy of febuxostat. Oxidation of febuxostat leads to three pharmacologically active metabolites, formed primarily by CYP450 isoforms: 1A1, 1A2, 2C8, or 2C9. These oxidative metabolites also undergo glucuronide conjugation to form inactive metabolites. While the glucuronide conjugates are eliminated in the urine, less than 4% of orally administered febuxostat is eliminated in the urine as unchanged drug. Therefore, since febuxostat is almost entirely eliminated by liver metabolism and the majority of metabolites that are eliminated in the urine are not active, renal impairment does not have a major impact on the elimination of febuxostat from the plasma.

For comparison, allopurinol is rapidly eliminated from the plasma via oxidative metabolism by XO in the liver to its primary metabolite, oxypurinol. The efficacy of allopurinol is largely due to oxypurinol, which, unlike the parent drug, is eliminated almost entirely by the kidneys (urinary excretion). Therefore, although elimination of allopurinol from the plasma is not reduced in subjects with renal impairment (because allopurinol is metabolized by the liver), the elimination from plasma that of its active metabolite oxypurinol, is reduced (because it is eliminated by the kidney). A linear relationship between the renal clearance of oxypurinol and creatinine clearance (a measure of kidney function) has been shown for subjects with renal impairment. This means that, as kidney function decreases, oxypurinol levels in the blood increase proportionally.[64]

5.2 Pharmacokinetics and Pharmacodynamics in Special Populations

Neither the pharmacokinetics (PK) nor the pharmacodynamics (PD) of febuxostat was substantially affected by differences in age or gender or by various degrees of mild to moderate hepatic impairment. Similarly, the percent decrease in sUA level was comparable regardless of renal function, even though exposure to febuxostat and some of its metabolites increased with increasing degrees of renal impairment. Therefore, dose adjustments for febuxostat based on differences in age (in adults), gender, or mild to moderate hepatic or renal impairment are not necessary. Since febuxostat was not administered to subjects with severe hepatic impairment (Child Pugh Class C), and only to a limited number of subjects with severe renal impairment (CrCl <30 mL/min), caution should be exercised when administering febuxostat to subjects with severe hepatic or severe renal impairment.

Population pharmacokinetic analyses from the FOCUS Study and a subset of subjects from the APEX Study indicate that the pharmacokinetics and pharmacodynamics of febuxostat in subjects with gout were consistent with Phase 1 data in healthy subjects.

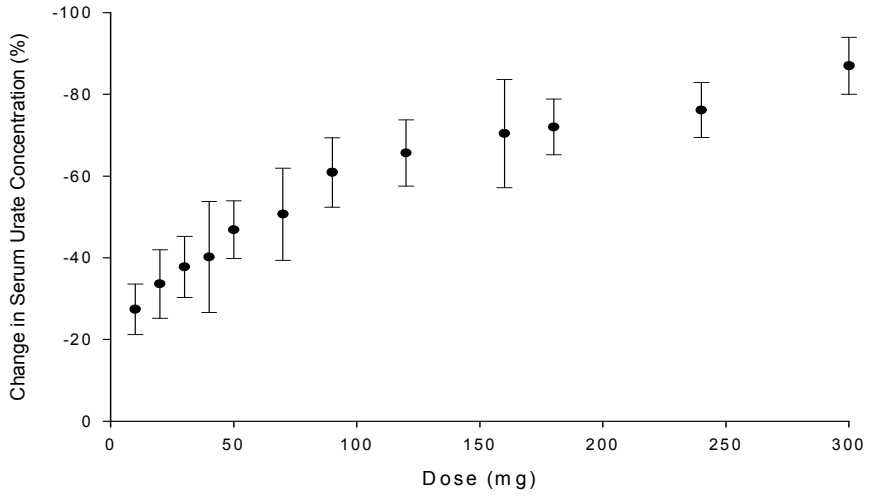
5.3 Pharmacodynamics

5.3.1 Effect on Urate, Xanthine and Hypoxanthine Levels

Febuxostat decreases sUA in both healthy subjects and in subjects with hyperuricemia and gout. In healthy subjects, the dose-response relationship appeared to be linear for febuxostat doses

ranging from 10 to 120 mg but the effect appeared to level off for doses above 120 mg (Figure 3). The sample sizes ranged from 7 to 18 subjects across the doses.

Figure 3 Dose-Response Effect on sUA Levels (Mean ± SD) in Healthy Subjects



Steady-state trough sUA concentrations were generally achieved within the first week of dosing with febuxostat. Following multiple administration of 10 mg - 300 mg febuxostat doses, mean serum urate concentrations in healthy subjects decreased by approximately 27% - 87% from baseline values. In conjunction with the decreases in serum urate concentrations, there was also a decrease in total daily urinary excretion and urinary concentration of uric acid. Mean serum xanthine concentrations increased following the administration of febuxostat, and there was also an increase in total daily urinary excretion, urinary concentration, and renal clearance of xanthine. Unlike serum xanthine concentration, no large increases in serum hypoxanthine concentrations were noted following febuxostat administration, likely due to the increased renal clearance of hypoxanthine.

5.3.2 Effect on Cardiac Repolarization (QTc Studies)

The effect of febuxostat on cardiac repolarization as assessed by the QTc interval was evaluated in normal healthy subjects and in subjects with gout. Febuxostat in doses up to 300 mg QD, at steady state, did not cause prolongation of the QTc interval. The Phase 1 QTc study had a

randomized, double-blind, 4-period crossover design and exposed healthy subjects randomly to 4 days of febuxostat 80 mg, febuxostat 300 mg, placebo, or moxifloxacin 400 mg (active control). Forty-one subjects completed all four treatment periods. The mean of the maximum postdose QTcF interval values for moxifloxacin 400 mg was statistically significantly greater than placebo ($p<0.001$) on Days 1 and 4, while there was no statistically significant difference between either of the febuxostat doses and placebo on either Day 1 or Day 4.

In the QTc Phase 1 study, the number of subjects with QTcF increases between 30 and 60 msec from baseline to Day 4 were 3 (7%), 3 (7%), and 19 (46%) for febuxostat 80 mg and 300 mg and moxifloxacin 400 mg, respectively, compared to 3 (7%) for placebo.

5.4 Drug-Drug Interaction Potential

Drug-drug interactions based on changes in protein binding are unlikely with febuxostat. In vitro protein-binding studies indicated that warfarin, digoxin, ibuprofen, captopril, bezafibrate, verapamil, and nitrendipine did not affect the protein binding of febuxostat in human plasma. An in vitro human hepatocyte enzyme-induction study showed that febuxostat was not associated with induction of CYP450 isoforms 1A1/2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4/5, and therefore, there is low potential for in vivo drug-drug interactions with febuxostat due to induction of liver CYP450.

Studies indicated that colchicine, indomethacin, naproxen, and hydrochlorothiazide do not have clinically significant effects on the PK of febuxostat, and therefore, no dose adjustment for febuxostat is necessary when it is coadministered with these drugs. Likewise, studies demonstrated that febuxostat has no clinically significant effects on the PK of indomethacin, naproxen, or colchicine, and therefore, no dose adjustment for these drugs is considered necessary when they are coadministered with febuxostat. In addition, a drug-drug interaction study demonstrated that febuxostat has little inhibitory effect on desipramine, a CYP2D6 substrate. Therefore, no dose adjustment is considered necessary for drugs that are CYP2D6 substrates when they are coadministered with febuxostat.

Two drug-drug interaction studies demonstrated that multiple doses of febuxostat have no clinically significant effects on the PK or PD of concomitantly administered warfarin. Both studies were of similar design. The second study increased the number of subjects, increased the duration of the warfarin lead-in period, and required a stable International Normalization Ratio (INR) of ≥1.5 to ≤2.0 for 3 days prior to subject randomization. These studies demonstrated that multiple oral doses of febuxostat 80 mg and 120 mg had no effect on the PK of R- or S-warfarin at steady-state. In addition, there was no effect on the PD of warfarin as measured by the maximum INR, 24-hour mean INR, and 24-hour mean Factor VII values. Furthermore, in these studies of healthy subjects, no safety concerns were associated with administration of multiple oral doses of febuxostat with warfarin. These studies support that no dose adjustment is necessary for warfarin when coadministered with febuxostat.

6 Clinical Development Program

6.1 Brief Regulatory and Development History of Febuxostat

Febuxostat has been studied for the treatment of hyperuricemia in subjects with gout. An NDA for febuxostat was filed in December 2004 by Takeda.

The recommended doses for febuxostat in the original NDA submission were 80 mg and 120 mg, based on data from a Phase 2 placebo-controlled study (Dose-Ranging), two Phase 3, adequate and well-controlled studies (APEX and FACT), and interim data from two open-label, long-term extension studies (FOCUS and EXCEL). Due to limited regulatory precedence on the conduct of clinical studies for the treatment of hyperuricemia in patients with gout, detailed discussions were held with FDA regarding all aspects of the study designs and agreements were reached on key design elements including control groups, duration, and the criteria for demonstration of superiority and non-inferiority to placebo or active control. In addition, an FDA Arthritis Advisory Committee (AAC) meeting was held in June 2004 during which aspects of clinical trials for chronic gout drugs were discussed. Recommendations from this AAC meeting regarding clinical trials in gout patients aligned with the conduct of the febuxostat clinical development program, including the use of sUA levels as an appropriate measure of efficacy.

Following the initial application, the FDA requested that the safety profile be examined further due to an imbalance in the number of cardiovascular/thrombotic adverse events reported for febuxostat compared to allopurinol or placebo. Takeda submitted results of an independent adjudication of the CV events reported in the Phase 2 and 3 and long-term studies, along with additional data from the ongoing long-term studies.

The FDA subsequently requested additional clinical data to more clearly characterize the potential CV risks of febuxostat 80 mg and to evaluate a lower dose of febuxostat (40 mg) to ensure that dose level(s) with favorable risk-benefit characterization would be defined. Based on discussions with FDA, an additional Phase 3 controlled study with a 6-month treatment period was conducted comparing febuxostat 40 mg and 80 mg with allopurinol for the management of hyperuricemia in subjects with gout (CONFIRMS). The CONFIRMS Study included special focus on cardiovascular/thrombotic AEs by prospectively adjudicating CV AEs based on the APTC criteria[19] later modified by White, et al.[20]

Results from the CONFIRMS Study demonstrated that 40 mg and 80 mg were both effective in lowering sUA. Therefore, Takeda is no longer pursuing the 120 mg dose for approval. In addition, prior discussions with the FDA highlighted that 40 mg data from the Phase 2 Dose-Ranging and the CONFIRMS Studies would be adequate to establish efficacy of the 40 mg dose.

The results of the CONFIRMS Study and the safety and efficacy data from the completed development program support the recommendation of febuxostat 40 mg and 80 mg for the treatment of hyperuricemia in subjects with gout.

6.2 Overview of Clinical Studies

The objective of the clinical development program was to evaluate the safety and efficacy of febuxostat for the management of hyperuricemia in patients with gout. Comparisons were made with placebo in the initial studies and allopurinol in later studies. Allopurinol is the only XO inhibitor approved in the USA for treatment of hyperuricemia in patients with gout.

As part of the USA development program, 31 clinical studies were conducted with febuxostat: 25 Phase 1 studies, one Phase 2 controlled, double-blind study, three Phase 3 controlled, double-blind studies, and two open-label, long-term extension studies.

All controlled Phase 2 and 3 studies enrolled subjects who had a history of gout and sUA levels ≥8.0 mg/dL. Exclusion criteria were similar across the controlled studies and included secondary hyperuricemia, severe renal impairment, active liver disease, or clinical instability due to a significant medical condition. Prophylaxis for gout flare was used for varying lengths of time across studies. The primary efficacy variables are summarized in Table 3 and the secondary efficacy variables are included in Table 6. Safety assessments were those routinely used in clinical studies and included adverse events (AEs), physical examinations, clinical laboratory variables, vital signs, and 12-lead ECGs.

The first randomized, controlled study was the Phase 2, placebo-controlled Dose-Ranging Study, which had a 28-day double-blind treatment period. Subjects (N=153) were randomized to receive placebo, febuxostat 40 mg, febuxostat 80 mg, or febuxostat 120 mg QD. Prophylaxis for gout flare was given from Day -14 to Day 14.

Subjects who completed the Dose-Ranging Study were eligible to enroll in the open-label, long-term extension study called FOCUS. In this study, subjects initially received febuxostat 80 mg with dose adjustments to either 40 mg or 120 mg to achieve and maintain sUA between 3.0 and 6.0 mg/dL. Dose changes were allowed up to 3 times, between Weeks 4 and 24 to manage efficacy, adverse events, or at the investigator's discretion. Subjects were to be on a stable dose for four continuous weeks by Week 28. If the subject did not achieve the target sUA level of <6.0 mg/dL during the first 24 weeks, the subject was to be discontinued from treatment. Subjects in this study could have received febuxostat for up to 5 years, and the study ended in December 2006.

The next 2 randomized controlled studies were Phase 3, APEX and FACT Studies. The APEX Study was a Phase 3, randomized, multicenter, allopurinol- and placebo-controlled study with a 28-week double-blind treatment period. After a 2-week screening period, 1072 subjects were

stratified by renal function and randomized in a 1:2:2:1:2 ratio to receive QD placebo, febuxostat 80 mg, febuxostat 120 mg, febuxostat 240 mg, or allopurinol 300 mg (100 mg if serum creatinine was >1.5 but ≤2.0 mg/dL, per allopurinol package insert). Fewer subjects were randomized to the placebo and febuxostat 240 mg groups to limit placebo subjects from further disease progression and to evaluate 2-times the originally planned febuxostat dose (120 mg). Per the published literature for prophylaxis at the time,[7] prophylaxis for gout flare was given from Day -14 (for those washing out of sUA lowering therapy) or Day 1 (for all others) through Week 8.

The FACT Study was a Phase 3, multicenter, randomized, allopurinol-controlled study with a 52-week double-blind treatment period. As is customary in chronic arthritis studies of >6 months duration when there is an available treatment option, subjects were not assigned to receive placebo. Subjects (N=760) were randomized in a 1:1:1 ratio to febuxostat 80 mg, febuxostat 120 mg, and allopurinol 300 mg QD. As in the APEX Study, prophylaxis for gout flare was given from Day -14 (for those washing out of urate lowering therapy) or Day 1 (for all others) through Week 8.

Subjects who completed the APEX and FACT studies were able to enroll in the open-label, long-term (up to 40 months) extension study, the EXCEL Study. The first 351 subjects enrolled under the original protocol initially received febuxostat 80 mg. At the request of the FDA, the protocol was amended to introduce an allopurinol control group, with randomization to include 80 mg and 120 mg, and allopurinol treatment groups. The additional subjects (n=735) were randomly assigned in a 2:2:1 ratio to receive febuxostat 80 mg, febuxostat 120 mg, or allopurinol (300/100 mg depending on renal function status). Subjects starting at a given treatment could be switched to another dose of febuxostat or another treatment to achieve and maintain sUA between 3.0 and 6.0 mg/dL, to manage adverse events, or at the investigator's discretion. The goal was to achieve a stable dose that would maintain sUA <6.0 mg/dL; if this was not achieved after 6 months, the subject was to be discontinued from the study. This study was stopped in December 2006 prior to initiation of the next Phase 3 controlled, double-blind study.

The third Phase 3 controlled study was the CONFIRMS Study, an active-controlled study with a 6-month double-blind treatment period. Based on published literature,[40] prophylaxis for gout flare was given for the entire treatment period of 6 months. The study was designed to evaluate the efficacy and safety of a lower dose, febuxostat 40 mg, and febuxostat 80 mg compared to allopurinol. Subjects (N=2269) were randomized in a 1:1:1 ratio to QD febuxostat 40 mg, febuxostat 80 mg, or allopurinol 300/200 mg (depending on renal function status). Randomization was stratified by baseline renal function (normal and mild; moderate) and previous completion of one of the long-term extension studies (FOCUS or EXCEL Studies).

The CONFIRMS Study evaluated subjects with renal impairment and prespecified that subjects would be categorized by renal function status using a protocol-defined formula. The renal function subgroups were: normal renal function as CrCl ≥90 mL/min; mild renal impairment as CrCl 60 - 89 mL/min; and moderate renal impairment as CrCl 30 - 59 mL/min, where CrCl was calculated using the Cockcroft-Gault formula corrected for ideal body weight (IBW) at screening.[65] This formula was used retrospectively to recalculate renal function and to categorize subjects in the APEX and FACT Studies.

Also the CONFIRMS Study was the only study that specified prospective adjudication of CV events by an independent committee and used a Data Monitoring Committee to review safety data during the study. The adjudication of CV events was done retrospectively for the APEX and FACT studies.

Table 3 provides a tabular summary of study designs for the Phase 2 and 3 controlled studies and the open-label, long-term extension studies. Graphic presentations of the study designs for these studies are provided in Appendix 2.

Table 3 Overview of Phase 2 and 3 Studies in Febuxostat Clinical Development Program

Study # Acronym ID	Treatment Groups	Design	N[a]	Duration of Treatment	Duration of Gout Flare Prophylaxis During Treatment	Study Population/Exclusion Criteria	Primary Efficacy Endpoint
Randomized, Double-Blind Phase 2 Study							
TMX-00-004 **Dose-Ranging Study**	Febuxostat: 40 mg (N=37) 80 mg (N=40) 120 mg (N=38) Placebo (N=38)	Randomized double-blind, parallel-group, placebo-controlled	153	4 weeks (option to continue in FOCUS)	2 weeks (colch)[f]	Male or female subjects between 18 and 85 years of age, sUA ≥8.0 mg/dL on the Day -2 Visit; history or presence of gout[g] and normal renal function. Exclusion criteria included alcohol abuse, and active liver disease or hepatic dysfunction.	The proportion of subjects with sUA <6.0 mg/dL after treatment with study drug (Day 28).
Randomized, Controlled, Double-Blind Phase 3 Studies							
C02-009 **APEX**	Febuxostat: 80 mg (N=267) 120 mg (N=269) 240 mg (N=134) Allopurinol 300/100 mg [c] (N=268) Placebo (N=134)	Randomized double-blind, parallel-group, active- and placebo-controlled	1072	28 weeks (option to continue in EXCEL)	8 weeks (colch or naprox)[e]	Male or female subjects between 18 and 85 years of age, with sUA ≥8.0 mg/dL on the Day -2 Visit; history or presence of gout.[66] Exclusion criteria included liver disease or active liver dysfunction, severe renal dysfunction, and alcohol abuse.	The proportion of subjects with last 3 sUA levels <6.0 mg/dL.

AEs=adverse events; colch=colchicine; naprox=naproxen.

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

b Subjects with normal renal function and mild renal impairment randomized to allopurinol received 300 mg , and subjects with moderate renal impairment randomized to allopurinol received allopurinol 200 mg . Febuxostat doses were not adjusted based on renal function.

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

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

e Prophylactic medications were colchicine 0.6 mg QD or naproxen 250 mg BID.

f Prophylactic medication was colchicine 0.6 mg BID.

g Wallace SL, Robinson H, Masi AT, et al. Preliminary criteria for the classification of the acute arthritis of primary gout. *Arthritis Rheum*. 1977;20:895-900.

Table 3 Overview of Phase 2 and 3 Studies in Febuxostat Clinical Development Program (continued)

Study # Phase Acronym ID	Treatment Groups	Design	N[a]	Duration of Treatment	Duration of Gout Flare Prophylaxis During Treatment	Study Population / Exclusion Criteria	Primary Efficacy Endpoint
Randomized, Controlled, Double-Blind Phase 3 Studies (continued)							
C02-010 **FAC**T	Febuxostat: 80 mg (N=256) 120 mg (N=251) Allopurinol 300 mg (N=253)	Randomized, double-blind, parallel-group, active-controlled	760	52 weeks (option to continue in EXCEL)	8 weeks (colch or naprox)[e]	Male or female subjects between 18 and 85 years of age, with sUA ≥8.0 mg/dL on the Day -2 Visit; history or presence of gout.[g] Exclusion criteria included liver disease or active liver dysfunction, abnormal renal function, and alcohol abuse.	The proportion of subjects with last 3 sUA levels <6.0 mg/dL.
F-GT06-153 **CONFIRMS**	Febuxostat: 40 mg (N=757) 80 mg (N=756) Allopurinol 300/200 mg[b] (N=756)	Randomized, double-blind, multicenter, active-controlled	2269	6 months	6 months (colch or naprox and lanso)[f]	Male or female subjects between 18 and 85 years of age, an sUA ≥8.0 mg/dL on the Day -4 Visit; history or presence of gout.[g] Exclusion criteria included clinically unstable myocardial infarction or stroke, liver disease or active live dysfunction, alcohol abuse, and estimated CrCl<30 mL/min.	The proportion of subjects with sUA <6.0 mg/dL at the Final Visit.

AEs=adverse events; colch=colchicine; naprox=naproxen.

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

b Subjects with normal renal function and mild renal impairment randomized to allopurinol received 300 mg , and subjects with moderate renal impairment randomized to allopurinol received allopurinol 200 mg . Febuxostat doses were not adjusted based on renal function.

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

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

e Prophylactic medications were colchicine 0.6 mg QD or naproxen 250 mg BID.

f Prophylactic medications were colchicine 0.6 mg QD or naproxen 250 mg BID and lansoprazole 15 mg QD.

g Wallace SL, Robinson H, Masi AT, et al. Preliminary criteria for the classification of the acute arthritis of primary gout. Arthritis Rheum. 1977;20:895-900.

Table 3 Overview of Phase 2 and 3 Studies in Febuxostat Clinical Development Program (continued)

Study # Acronym ID	Treatment Groups	Design	N[a]	Duration of Treatment	Duration of Gout Flare Prophylaxis During Treatment	Study Population / Exclusion Criteria	Primary Efficacy Endpoint
Open-Label, Long-Term Extension Studies							
TMX-01-005 **Phase 2** **FOCUS**	Febuxostat: 40 mg (N=8) 80 mg (N=79) 120 mg (N=29) (All subjects started on 80 mg; N = number at stable dose)	Open-label, safety extension that allowed switching between treatment groups	116	Up to 5 years	4 weeks (colch)[f]	Subjects who completed the Phase 2 Dose-Ranging Study.	The proportion of subjects with sUA decreased to or maintained at <6.0 mg/dL.
C02-021 **Phase 3** **EXCEL**	Febuxostat: 80 mg (N=606) 120 mg (N=388) Allopurinol 300/100 mg [d] (N=92) (N = number of subjects at stable dose)	Randomized, open-label, active-controlled, safety extension that allowed switching between treatment groups	1086	Up to 40 months	8 weeks (colch or naprox)[e]	Subjects who completed Studies APEX or FACT.	The proportion of subjects with sUA <6.0 mg/dL.

AEs=adverse events; colch=colchicine; naprox=naproxen.

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

b Subjects with normal renal function and mild renal impairment randomized to allopurinol received 300 mg , and subjects with moderate renal impairment randomized to allopurinol received allopurinol 200 mg . Febuxostat doses were not adjusted based on renal function.

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

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

e Prophylactic medications were colchicine 0.6 mg QD or naproxen 250 mg BID.

f Prophylactic medication was colchicine 0.6 mg BID.

7 Clinical Efficacy

7.1 Overview of Efficacy

Febuxostat is effective in treating hyperuricemia in subjects with gout based on results from the four randomized double-blind, controlled Phase 2 and 3 studies (Dose-Ranging Study, APEX, FACT, and CONFIRMS) and the two open-label long-term extension studies (FOCUS and EXCEL). These studies were conducted in 4254 subjects with hyperuricemia (sUA ≥8 mg/dL) and a diagnosis of gout according to the American Rheumatism Association (ARA) criteria. The data from these studies support the following conclusions:

- Febuxostat 40 mg is more efficacious than placebo and similar to allopurinol in the ability to lower sUA levels to <6.0 mg/dL.
- Febuxostat 80 mg is superior to allopurinol and febuxostat 40 mg in the ability to lower sUA levels <6.0 mg/dL. The benefit was particularly pronounced in subjects with tophi or sUA ≥10.0 mg/dL.
- In subjects with mild-to-moderate renal impairment, both recommended doses of febuxostat (40 mg and 80 mg) showed enhanced efficacy in lowering sUA when compared to allopurinol.
- Long-term treatment with febuxostat maintained the reduction in sUA, reduced the incidence of gout flares to almost zero, and resulted in resolution of tophi.

7.2 Efficacy Studies

7.2.1 Demographics and Baseline Characteristics

Subjects enrolled in the febuxostat clinical program were representative of the population that is likely to use febuxostat following approval. Most subjects in the controlled studies were male (94%), the majority reported the use of alcohol (67%), and over one-half (63%) were obese (BMI ≥30 kg/m^2). One-half of the randomized subjects had a history of hypertension (50%), and approximately one-third a history of hyperlipidemia (38%). On average, subjects had a history of gout for ≥10 years, 36% of subjects had a baseline sUA ≥10.0 mg/dL, 23% had a history or presence of a tophus, and 60% of subjects had mild-to-moderate renal impairment.

No clinically relevant differences were observed across treatment groups for any demographic or baseline characteristic within a study. Table 4 and Table 5 provide summaries of important demographic and baseline variables for all subjects within each study to allow comparison across the four controlled Phase 2 and 3 studies that are pivotal in assessing efficacy.

Table 4 Subject Demographics and Baseline Characteristics - All Subjects in All Treatment Groups (Phase 2 and 3 Controlled Studies)

Variable	Dose-Ranging All Subjects (N=153) n (%)	APEX All Subjects (N=1072) n (%)	FACT All Subjects (N=760) n (%)	CONFIRMS All Subjects (N=2269) n (%)
Gender				
Male	136 (89)	1005 (94)	729 (96)	2141 (94)
Race				
Asian	2 (1)	26 92)	25 (30)	88 (4)
Black or African American	11 (7)	120 (11)	62 (8)	228 (10)
White	134 (88)	835 (78)	587 (77)	1863 (82)
American Indian or Alaskan Native	0	1 (<1)	1 (<1)	22 (<1)
Native Hawaiian or Other Pacific Islander	0	20 (2)	18 (2)	32 (1)
Other	6 (4)	70 (7)	67 (9)	34 (1)
Age (years)				
<45	37 (24)	312 (29)	230 (30)	568 (25)
45-<65	80 (52)	597 (56)	398 (52)	1327 (59)
≥65	36 (24)	163 (15)	132 (17)	374 (17)
Mean ± SD	54.0 ± 12.69	51.5 ± 12.17	51.8 ± 12.13	52.8 ± 11.73
Range	23 - 80	22 - 84	23 - 83	19 - 85
Years with Gout				
Mean ± SD	N/A	10.9±8.96	11.9 (9.56)	11.6±9.31
Range	N/A	<1-41	<1-51	<1-53
Baseline Serum Urate				
<9.0 mg/dL	46 (33)	285 (27)	207 (27)	837 (37)
9.0 - <10.0 mg/dL	47 (34)	366 (34)	236 (31)	699 (31)
10.0 - <11.0 mg/dL	42 (30)	221 (21)	181 (24)	454 (20)
11.0 - <12.0 mg/dL	--	125 (12)	87 (12)	189 (8)
≥12.0 mg/dL	5 (4)	70 (7)	45 (6)	90 (4)
Mean ± SD	9.66 ± 1.20	9.9 ± 1.26	9.8 ± 1.24	9.6 ± 1.18
History or Presence of Tophus	36 (24)	299 (28)	186 (24)	478 (21)

N/A = not available.

Table 5 Baseline Medical Conditions - All Subjects (Phase 2 and 3 Controlled Studies)

Medical Condition	Phase 2 Dose-Ranging All Subjects (N=153) n (%)	APEX All Subjects (N=1072) n (%)	FACT All Subjects (N=760) n (%)	CONFIRMS All Subjects (N=2269) n (%)
At least one of the following Medical Conditions:	100 (65)	649 (61)	462 (61)	1526 (67)
Atherosclerotic Disease	14 (9)	145 (14)	75 (10)	261 (12)
Congestive Heart Failure	4 (3)	31 (3)	10 (1)	49 (2)
Diabetes	13 (8)	90 (8)	53 (7)	312 (14)
Hypertension	75 (49)	508 (47)	333 (44)	1199 (53)
Hyperlipidemia	70 (46)	352 (33)	258 (34)	942 (42)
Myocardial Infarction	4 (3)	53 (5)	23 (3)	90 (4)
Stroke	3 (2)	22 (2)	6 (<1)	8 (<1)
Transient Ischemic Attack	1 (<1)	9 (<1)	6 (<1)	29 (1)
Lifestyle Risk Factor				
BMI ≥30 kg/m^2	94 (61)	662 (62)	472 (62)	1442 (64)
Alcohol Drinker	97 (63)	709 (66)	502 (66)	1549 (68)
Tobacco User	30 (20)	216 (20)	131 (17)	410 (18)
Low-Dose Aspirin Use[a]	0	185 (17)	125 (16)	405 (18)
Creatinine Clearance (mL/min)[b]				
≥90 (normal)	25 (16)[c]	541 (51)	371 (49)	786 (35)
60-89 (mild impairment)	80 (52)	377 (35)	295 (39)	1081 (48)
30-59 (moderate impairment)	47 (31)	154 (14)	94 (12)	402 (18)

a Defined as a total dose <325 mg/day that was ongoing at the time of study completion.
b Values are for estimated creatinine clearance. The baseline renal function of subjects in the Dose-Ranging, APEX, and FACT studies were re-evaluated based on current published guidelines and criteria used in the CONFIRMS Study.
c One subject had a missing value for the Dose-Ranging Study.

7.2.2 Efficacy Endpoints

The primary and secondary endpoints are summarized in Table 6. While there were slight differences in their definitions, the endpoints were generally similar and consistent across studies. The Final Visit sUA level was used as the primary endpoint for CONFIRMS, because in the APEX and FACT Studies, the results of treatment comparisons for the endpoint of the Final Visit were consistent with those obtained for the endpoint of the last 3 sUA levels.

Table 6 Efficacy Primary and Secondary Endpoints (Phase 2 and 3 Controlled Studies)

Study	Primary Endpoint	Secondary Endpoints
Dose-Ranging Study (Phase 2)	Proportion of subjects with sUA levels <6.0 mg/dL at end of treatment (Day 28)	Proportion of subjects with sUA <6.0 mg/dL at different time intervals; percent reduction in sUA levels from baseline at those time intervals; maximum percent reduction in sUA level during treatment; percent reduction in 24-hour urine uric acid level at end of study.
APEX (Phase 3)	Proportion of subjects with last 3 sUA levels <6.0 mg/dL	Proportion of subjects with sUA <6.0 mg/dL at Final Visit; percent reduction in sUA levels; percent reduction in primary tophus size; reduction in total number of tophi in subjects with palpable tophi at baseline; proportion of subjects requiring treatment for gout flare between Weeks 8 and 28.
FACT (Phase 3)	Proportion of subjects with last 3 sUA levels <6.0 mg/dL	Proportion of subjects with sUA <6.0 mg/dL at Final Visit; percent reduction in sUA levels; percent reduction in primary tophus size; reduction in total number of tophi in subjects with palpable tophi at baseline; proportion of subjects requiring treatment for gout flare between Weeks 8 and 52.
CONFIRMS (Phase 3)	Proportion of subjects with sUA level <6.0 mg/dL at the Final Visit	Proportion of subjects with renal impairment; proportion of subjects with sUA <6.0 mg/dL at each visit; proportion of subjects with sUA <6.0 mg/dL at each visit; percent reduction in sUA levels at each visit.

Serum Urate Levels

Serum urate was analyzed (using the enzymatic method) as part of the standard chemistry panel at a central laboratory. Serum urate levels were blinded to Takeda, the investigator and subject, after the Day -4 Visit and throughout the duration of the study.

Gout Flare

Gout flares are expected to occur in the first weeks and months after initiation of ULT, independent of the therapeutic agent. Per protocol, all subjects received prophylaxis for a specified time period that differed across studies. Subjects were instructed to report gout flares and the investigator treated the flare as appropriate, using the following medications: NSAIDs, colchicine, pain medication, and/or corticosteroids.

Tophus Assessment

In the APEX, FACT, and EXCEL Studies, if a subject had tophi at baseline, a primary palpable tophus was selected and measured.[67] High variability in the tophus size measurements was observed. Natural fluctuations in tophus size over time, the lack of a limit on the maximum size allowed, changes in site personnel measuring tophi over the course of the studies, and differences in the ability of the raters to measure the same tophus reproducibly over time all contributed to the overall variation in the tophus measurements. Presence or absence of tophi is easy to evaluate, and based on the presence or absence of the primary tophus, resolution of tophi was assessed at each visit in the long-term extension studies.

7.2.3 Statistical Methodology - Phase 2 and 3 Controlled Studies

Efficacy analyses in the Phase 2 and 3 controlled studies were performed using a modified intent-to-treat (ITT) population, which was defined as all randomized subjects who took at least one dose of study drug and who had a baseline sUA level ≥8.0 mg/dL. Thirteen subjects (evenly distributed across four treatment groups) were excluded in the Dose-Ranging Study because their sUA samples were collected out of window; 10 subjects were excluded across the Phase 3 controlled studies for sUA levels <8.0 mg/mL just prior to randomization. Subjects receiving any dose of allopurinol (300, 200, or 100 mg) were analyzed together. This was done (as an *a priori* decision) based on the knowledge that subjects with renal impairment given lower doses (200 or 100 mg) were expected to achieve higher plasma levels of active metabolite.[64,68]

All statistical tests and confidence intervals (CI) were 2-sided and all computations were performed prior to rounding unless otherwise specified. All statistical tests and confidence intervals will be two-sided and conducted at the 0.05 significance level, unless otherwise specified.

In the Phase 3 controlled studies, comparisons for the primary efficacy variable to allopurinol were done sequentially using a closed testing procedure within each of 2 steps. In the 1st step, the febuxostat groups were compared to the allopurinol group to test for non-inferiority. In the 2nd step, each febuxostat treatment group shown to be non-inferior to allopurinol was tested for

superiority to allopurinol. Since comparisons were done sequentially using a closed testing procedure within each step, adjustments to the overall alpha level were made only within each set of comparisons.

See Appendix 3 for more details on sample size calculations and statistical methods for the primary efficacy endpoints for each of the Phase 2 and 3 controlled studies.

7.2.4 Phase 2 Dose-Ranging Study - Efficacy Results

The objective of the Phase 2 Dose-Ranging Study was to select a dose(s) of febuxostat that safely and effectively decreased sUA levels in subjects with hyperuricemia and gout. Based on safety and PK data from Phase 1 studies, febuxostat QD doses of 40 mg, 80 mg and 120 mg were selected. The treatment period was 28 days. The efficacy endpoints were described in Table 6.

Subject Disposition

One hundred fifty-three subjects were randomized and received at least 1 dose of study drug. Eight subjects discontinued from the study (Table 7).

Table 7 Subject Disposition (Phase 2 Dose-Ranging Study)

Subject Disposition	Placebo	Febuxostat			All Subjects
		40 mg	80 mg	120 mg	
All Randomized Subjects	38	37	40	38	153
Completed Study	36	36	37	36	145
Discontinued	2	1	3	2	8
Primary Reason:					
Adverse Event[a]	1	1	2	2	6
Gout Flare	1	0	0	0	1
Other	0	0	1[b]	0	1

a Discontinuations due to AEs are discussed in the Section 8.6.2.
b Subject noncompliant with study drug dosing.

The mean number of days on study drug was between 27.5 and 27.9 days across all treatment groups. Subjects received prophylaxis for gout flare during the first 2 weeks of treatment.

Serum Urate Levels

Compared to placebo, febuxostat at all 3 doses (40, 80, and 120 mg) significantly increased the proportion of subjects with sUA <6.0 mg/dL at the end of treatment (Day 28) (Table 8). The proportion of subjects with sUA <6.0 mg/dL increased with increasing dose of febuxostat.

Febuxostat's effectiveness, when compared to placebo, was apparent by Day 7 and was sustained at each visit (Day 14, 21, and 28).

Table 8 Proportion of Subjects With sUA <6.0 mg/dL at the End of Treatment - ITT Population (Phase 2 Dose-Ranging Study)

Subjects With sUA <6.0 mg/dL	Placebo (N=35)	Febuxostat 40 mg (N=34)	Febuxostat 80 mg (N=37)	Febuxostat 120 mg (N=34)
Final Visit	0% (0/35)	56% (19/34)[a]	76% (28/37)[a]	94% (32/34)[a]

a Statistically significantly different from placebo ($p<0.001$) using Fisher's exact test.

Gout Flare

The incidence of gout flares was similar between the placebo (37%) and febuxostat 40 mg (35%) groups. Among the febuxostat treatment groups, higher flare rates were observed at higher febuxostat doses (43% for 80 mg, and 55% for 120 mg). However, flares were notably lower during the interval when colchicine and febuxostat were coadministered than the interval when febuxostat was administered alone.

7.2.5 Phase 3 Controlled Studies - Efficacy Results

7.2.5.1 APEX Study - Efficacy Results

The objective of the APEX Study was to compare the safety and efficacy of different doses of febuxostat versus placebo and allopurinol in subjects with hyperuricemia and gout. The treatment period was 28 weeks. The primary and secondary efficacy variables were summarized in Table 6.

Subject Disposition

Subjects were randomized in 1:2:2:1:2 ratio to placebo, febuxostat 80 mg, febuxostat 120 mg, febuxostat 240 mg, and allopurinol, and 1072 subjects received at least 1 dose of study drug.

Overall, 28% (300/1072) of the subjects discontinued treatment (Table 9). A greater proportion of subjects in the febuxostat groups discontinued treatment due to gout flare compared to placebo and allopurinol groups, although no dose response trend was apparent.

The mean duration of exposure for ITT subjects in the placebo, febuxostat 80 mg, 120 mg, 240 mg and allopurinol groups was 23.3, 21.9, 23.9, 21.0 and 24.1 weeks, respectively. Subjects received prophylaxis for gout flare during the first 8 weeks of treatment.

Table 9 Subject Disposition (APEX Study)

Subject Disposition	Placebo (N=134) n (%)	Febuxostat 80 mg (N=267) n (%)	Febuxostat 120 mg (N=269) n (%)	Febuxostat 240 mg (N=134) n (%)	Allopurinol (N=268)[a] n (%)
Completed Study	101 (75)	174 (65)	200 (74)	86 (64)	211 (79)
Discontinued	33 (25)	93 (35)	69 (26)	48 (36)	57 (21)
Primary Reason:					
Lost to follow-up	10 (7)	19 (7)	17 (6)	9 (7)	17 (6)
Adverse events[b]	5 (4)	18 (7)	16 (6)	11 (8)	18 (7)
Personal reason(s)	9 (7)	16 (6)	16 (6)	9 (7)	9 (3)
Other	3 (2)	15 (6)	8 (3)	6 (4)	5 (2)
Gout flare	0	13 (5)	6 (2)	8 (6)	1 (<1)
Protocol violation	3 (2)	6 (2)	3 (1)	3 (2)	6 (2)
Therapeutic failure	3 (2)	6 (2)	3 (1)	2 (1)	1 (<1)

a Allopurinol 300 mg (n=258) and allopurinol 100 mg (n=10).
b Discontinuations due to AEs are discussed in the Section 8.3.6.

Serum Urate Levels

Each of the febuxostat 80 mg, 120 mg, and 240 mg groups had statistically significantly ($p<0.001$) greater proportions of subjects whose last 3 sUA levels were <6.0 mg/dL compared to allopurinol and placebo (Table 10). The response rates (sUA <6.0 mg/dL) at the Final Visit were 72%, 79%, and 92% in the febuxostat 80, 120, and 240 mg groups, respectively, compared to 39% in the allopurinol group and 1% in the placebo group (Table 11).

Table 10 Proportion of Subjects Whose Last 3 Serum Urate Levels Were <6.0 mg/dL - ITT Subjects (APEX Study)

Subjects With sUA <6.0 mg/dL	Placebo (N=134) n (%)	Febuxostat 80 mg (N=262) n (%)	Febuxostat 120 mg (N=269) n (%)	Febuxostat 240 mg (N=134) n (%)	Allopurinol (N=268) n (%)
Last 3 Visits	0	126 (48)[a,b,c]	175 (65)[a]	92 (69)[a,d]	60 (22)[a]
		Difference in Proportions		**97.5% CI[e]**	**P-value[f]**
Febuxostat 80 mg vs Allopurinol		26%		(16.7%, 34.7%)	<0.001[g]
Febuxostat 120 mg vs Allopurinol		43%		(34.0%, 51.3%)	<0.001[g]

CI=confidence interval.

a Statistically significant difference versus placebo ($p \leq 0.05$) (Hochberg's procedure for multiple comparisons was used for comparisons of the febuxostat treatment groups versus placebo).
b Statistically significant difference versus febuxostat 120 mg ($p \leq 0.05$).
c Statistically significant difference versus febuxostat 240 mg ($p \leq 0.05$).
d Statistically significant difference versus allopurinol 300/100 mg ($p \leq 0.05$).
e 97.5% confidence interval (CI) for difference in proportions based on normal approximation for binomial distribution.
f P-values from a Cochran-Mantel-Haenszel (CMH) test stratified by baseline renal function (serum creatinine ≤1.5 mg/dL vs >1.5 mg/dL).
g Statistically significant difference versus allopurinol 300/100 mg at the 0.05 level using Hochberg's procedure for multiple comparisons.

Table 11 Proportion of Subjects With Serum Urate <6.0 mg/dL at the Final Visit - ITT Subjects (APEX Study)

Subjects With sUA <6.0 mg/dL	Placebo n/N	Placebo (%)	Febuxostat 80 mg[a,b,c] n/N	Febuxostat 80 mg[a,b,c] (%)	Febuxostat 120 mg[a,b,c] n/N	Febuxostat 120 mg[a,b,c] (%)	Febuxostat 240 mg[a,b] n/N	Febuxostat 240 mg[a,b] (%)	Allopurinol[a] n/N	Allopurinol[a] (%)
Final Visit	1/127	(1)	183/253	(72)	209/265	(79)	116/126	(92)	102/263	(39)

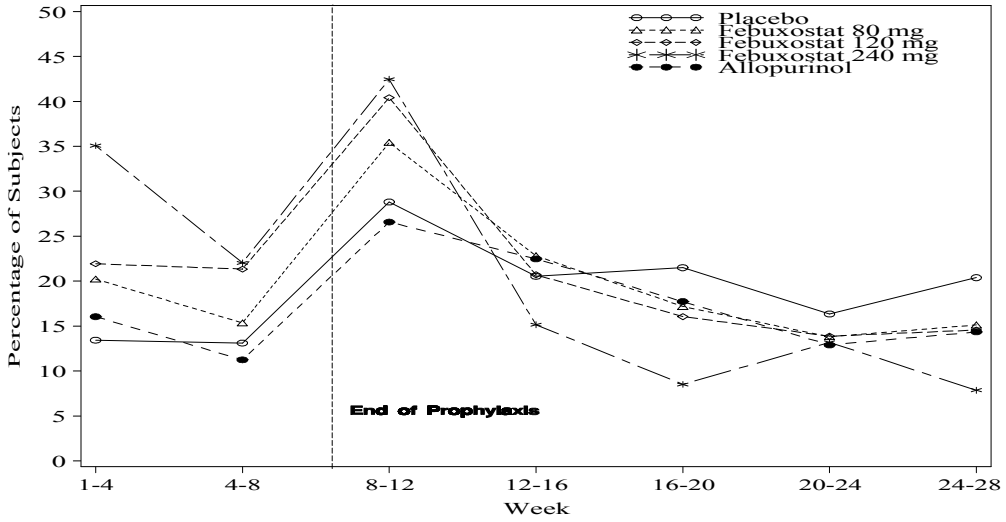
a Statistically significant difference versus placebo ($p \leq 0.05$).
b Statistically significant difference versus allopurinol 300/100 mg ($p \leq 0.05$).
c Statistically significant difference versus febuxostat 240 mg ($p \leq 0.05$).

Gout Flares

The majority of subjects received treatment for a gout flare at some point during the study (ranging from 51% to 66% across treatment groups). During the 8-week prophylaxis period, 20%-46% of subjects required treatment for a gout flare, with greater proportions of subjects in the febuxostat 120 mg and 240 mg groups requiring treatment. Flares increased immediately following the prophylaxis period and gradually decreased over time (Figure 4). There was no statistically significant difference across treatment groups in the proportion of subjects requiring treatment for a gout flare between Week 8 and Week 28, which ranged between 46% and 57%.

This number fell to between 8% and 20% of subjects during the last 4 weeks of the study (Weeks 24 to 28).

Figure 4 Gout Flares Over Time (APEX Study)



Interval (wk)	1-4	4-8	8-12	12-16	16-20	20-24	24-28
Placebo[a]	134	122	118	112	107	104	103
Feb 80 mg[a]	262	241	223	206	192	181	172
Feb 120 mg[a]	269	253	240	227	218	209	206
Feb 240 mg[a]	134	118	106	99	94	91	89
Allopurinol[a]	268	249	237	227	220	217	216

a Sample size for each time interval.

Tophi

At baseline 28% (299/1072) of APEX subjects had a palpable tophus (range across treatment groups: 24% - 33%). The median size of the primary palpable tophus was reduced, with a median percent change from baseline at Week 28 of -52.0%, -45.6%, -54.2%, -53.2%, and -31.5% in the placebo, febuxostat 80 mg, febuxostat 120 mg, febuxostat 240 mg, and allopurinol groups, respectively. (Because there were very small or large changes in tophus size from baseline, the median value is an appropriate summary.) Longer term treatment is necessary to see resolution of tophi.[10]

A decrease in the mean number of tophi was noted over time in each treatment group, with a mean change in number from baseline at Week 28 was -0.3, -0.3, -1.2, -0.4, and -0.4 tophi in the

placebo, febuxostat 80 mg, febuxostat 120 mg, febuxostat 240 mg, and allopurinol groups, respectively

7.2.5.2 FACT Study - Efficacy Results

The objective of the FACT Study was to compare the safety and efficacy of febuxostat 80 mg and 120 mg versus allopurinol in subjects with hyperuricemia and gout. The treatment period was 52 weeks. The primary and secondary efficacy variables are provided in Table 6.

Subject Disposition

Subjects were randomized in a 1:1:1 ratio to febuxostat 80 mg, febuxostat 120 mg, and allopurinol, and 760 subjects received at least 1 dose of study drug. Overall, 33% (252/760) of the subjects discontinued treatment (Table 12). A greater proportion of subjects in the febuxostat 120 mg group discontinued treatment due to gout flares compared to febuxostat 80 mg and allopurinol groups.

The mean duration of exposure for ITT subjects was 40.7, 37.8, and 43.2 weeks for febuxostat 80 mg, febuxostat 120 mg, and allopurinol groups, respectively. Subjects received prophylaxis for gout flare during the first 8 weeks.

Table 12 Subject Disposition (FACT Study)

	Febuxostat 80 mg (N=256) n (%)	**Febuxostat 120 mg (N=251) n (%)**	**Allopurinol[a] (N=253) n (%)**
Completed Study	168 (66)	153 (61)	187 (74)
Discontinued	88 (34)	98 (39)	66 (26)
Primary Reason:			
Lost to follow-up	25 (10)	18 (7)	21 (8)
Adverse event[b]	16 (6)	23 (9)	8 (3)
Gout flare	10 (4)	28 (11)	9 (4)
Personal reason(s)	19 (7)	13 (5)	13 (5)
Other	11 (4)	14 (6)	14 (6)
Protocol violation	7 (3)	2 (<1)	1 (<1)

a All allopurinol subjects received the 300 mg dose.
b Discontinuations due to AEs are discussed in Section 8.3.6.

Serum Urate Levels

Both the febuxostat 80 mg and 120 mg groups had significantly greater proportions of subjects achieving <6.0 mg/dL at the last 3 measurements compared to the allopurinol group ($p<0.001$) (Table 13). Both the febuxostat 80 mg and 120 mg treatment groups also had significantly greater ($p\leq0.05$) proportions of subjects with sUA <6.0 mg/dL at the Final Visit than the allopurinol group (Table 14).

Table 13 Proportion of Subjects With Last 3 sUA Levels <6.0 mg/dL - ITT Subjects (FACT Study)

Subjects With sUA <6.0 mg/dL	Febuxostat 80 mg (N=255) n (%)	Febuxostat 120 mg (N=250) n (%)	Allopurinol (N=251) n (%)
Last 3 Visits	136 (53)	154 (62)	53 (21)
	Difference in Proportions	97.5% CI[a]	P-value[b]
Febuxostat 80 mg vs Allopurinol	32%	(23.1%, 41.3%)	<0.001[c]
Febuxostat 120 mg vs Allopurinol	41%	(31.5%, 49.5%)	<0.001[c]

CI = confidence interval.
a 97.5% confidence interval for the difference in proportions based on the normal approximation for the binomial distribution.
b P-values from the Fisher's exact test.
c Statistical significance versus allopurinol at the 0.05 level based on Hochberg's procedure for multiple comparisons.

Table 14 Proportion of Subjects With sUA <6.0 mg/dL at the Final Visit - ITT Subjects (FACT Study)

Subjects With sUA <6.0 mg/dL	Febuxostat 80 mg[a] n/N (%)	Febuxostat 120 mg[a] n/N (%)	Allopurinol n/N (%)
Final Visit	185/249 (74)	193/242 (80)	88/242 (36)

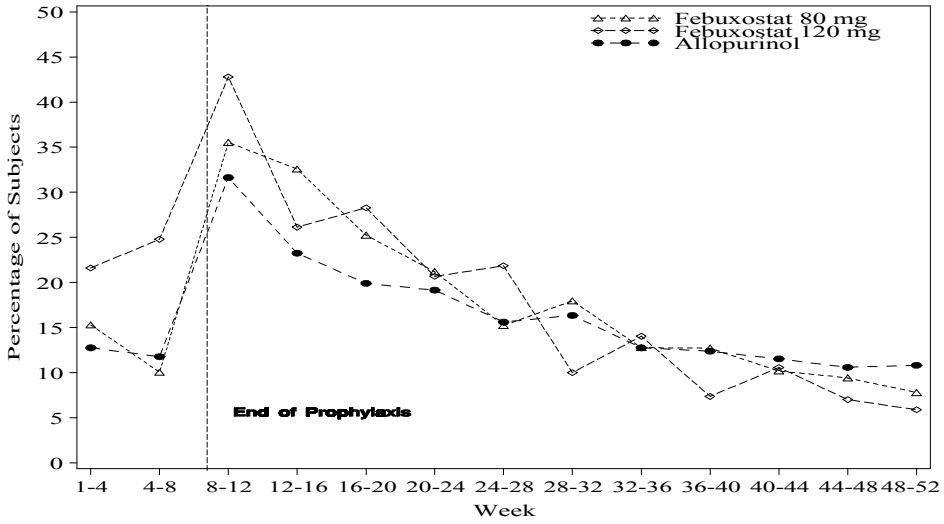
a Statistically significant difference versus allopurinol ($p\leq0.05$) using Fisher's exact test.

Gout Flares

The majority of subjects received treatment for gout flare at some point during the study (ranging from 64% to 72% across treatment groups). During the 8-week prophylaxis period, a statistically significantly greater proportion of subjects in the febuxostat 120 mg (36%) treatment group required treatment for a gout flare compared to both the febuxostat 80 mg (22%) and allopurinol 300 mg (21%) treatment groups. After the 8-week prophylaxis period, the incidences of flares

immediately increased, were generally similar across treatment groups, and gradually decreased over time (Figure 5). From Week 8 to Week 52, between 64% and 70% of subjects received treatment for gout flares. This number fell to between 6% and 11% during the last 4 weeks of the study (Weeks 48 to 52).

Figure 5 Gout Flares Over Time (FACT Study)



Interval (wk)	1-4	4-8	8-12	12-16	16-20	20-24	24-28	28-32	32-36	36-40	40-44	44-48	48-52
Feb 80 mg[a]	255	239	228	218	210	203	197	195	188	181	177	170	167
Feb 120 mg[a]	250	234	215	199	191	179	174	170	164	163	161	157	153
Allopurinol[a]	251	238	234	228	216	209	205	202	196	194	191	189	185

a Sample size for each time interval.

Tophi

At baseline 25% (185/760) of FACT subjects had a palpable tophus range across treatment group: 23%-26%). The median size of the primary palpable tophus was reduced, with a median percent change from baseline in the size of the primary palpable tophus at Week 52 of -83.4%, -65.5%, and -49.7% in the febuxostat 80 mg, febuxostat 120 mg, and allopurinol groups, respectively. (Because there were very small or large changes in tophus size from baseline, the median value is an appropriate summary.)

Among subjects with palpable tophi at baseline, no statistically significant differences were observed between treatments in the number of tophi at Week 52. The mean change in the number

of tophi from baseline at Week 52 was -0.4, -1.0, and -0.7 in the febuxostat 80 mg, febuxostat 120 mg, and allopurinol groups, respectively

7.2.5.3 CONFIRMS Study - Efficacy Results

The objective of the CONFIRMS Study was to compare the efficacy and safety of febuxostat 40 mg and 80 mg to allopurinol in subjects with hyperuricemia and gout. This study was a randomized, allopurinol-controlled, Phase 3 study with a 6-month treatment period. The primary and secondary efficacy variables are provided in Table 6.

Subject Disposition

Subjects were randomized in a 1:1:1 ratio to febuxostat 80 mg, febuxostat 120 mg, and allopurinol. A total of 2269 subjects received at least 1 dose of study drug, and 418 (18%) subjects discontinued the study (Table 15). Few subjects withdrew early due to gout flares in this study that required prophylaxis for gout flare throughout the 6-month treatment period.

Table 15 Subject Disposition (CONFIRMS Study)

Variable	Febuxostat 40 mg (N=757) n (%)	Febuxostat 80 mg (N=756) n (%)	Allopurinol[a] (N=756) n (%)
Number of Subjects Who Discontinued	125 (17)	158 (21)	135 (18)
Primary Reason for Discontinuation			
Adverse Events	49 (7)	61 (8)	64 (9)
Protocol Violation	10 (1)	2 (<1)	4 (1)
Personal reasons(s)	12 (2)	24 (3)	9 (1)
Lost to Follow-Up	28 (4)	33 (4)	28 (4)
Therapeutic Failure	1 (<1)	1 (<1)	1 (<1)
Withdrew Consent	14 (2)	20 (3)	16 (2)
Did not Meet Inclusion/Exclusion Criteria	0	2 (<1)	0
Gout Flare	3 (<1)	7 (1)	2 (<1)
Other	8 (1)	8 (1)	11 (2)

a 611 subjects received allopurinol 300 mg; 145 received allopurinol 200 mg.

The mean number of days on study drug in the febuxostat 40 mg, febuxostat 80 mg, and allopurinol treatment groups was 165.7 days, 160.5 days, and 163.2 days, respectively. Subjects received prophylaxis for gout flare during the duration of the 6-month treatment period.

Serum Urate Levels

The proportions of ITT subjects with Final Visit sUA levels <6.0 mg/dL were 45%, 67%, and 42% in the febuxostat 40 mg, febuxostat 80 mg, and allopurinol groups, respectively (Table 16). Febuxostat 40 mg was determined to be noninferior to allopurinol. The response rate of the febuxostat 80 mg group was significantly higher than both the febuxostat 40 mg ($p<0.001$) and allopurinol ($p<0.001$) groups.

Table 16 Proportion of Subjects With Final Visit sUA Level <6.0 mg/dL - ITT Subjects (CONFIRMS Study)

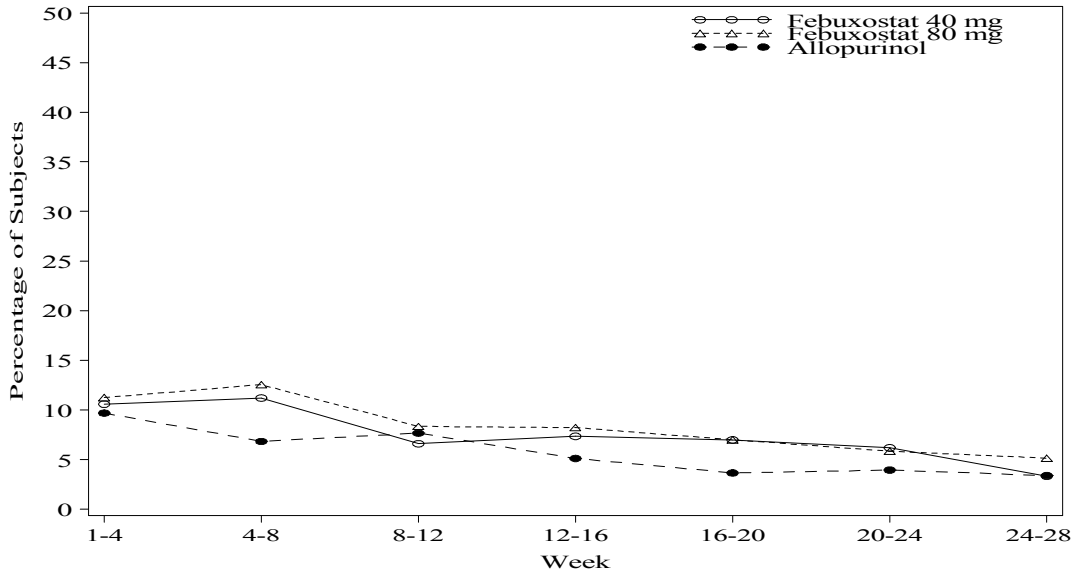
Subjects With sUA Level <6.0 mg/dL	Febuxostat 40 mg (N=757) n (%)	Febuxostat 80 mg (N=756) n (%)	Allopurinol 300/200 mg (N=755) n (%)
Final Visit	342 (45.2)	507 (67.1)	318 (42.1)
Comparison	**Difference in Proportions**	**95% CI[a]**	**P-value[c]**
Febuxostat 40 mg vs Allopurinol	3.1%[b]	(-1.9%, 8.1%)	0.233
Febuxostat 80 mg vs Allopurinol	24.9%	(20.1%, 29.8%)	<0.001[d]
Febuxostat 40 mg vs Febuxostat 80 mg	21.9%	(17.0%, 26.8%)	<0.001[d]

CI=confidence interval.
a 95% CI = 95% confidence interval for the difference in proportions based on the normal approximation for the binomial distribution.
b Febuxostat 40 mg statistically noninferior to allopurinol 300/200 mg.
c p-value from a Fisher's exact test.
d Statistically significant difference at the 0.001 level.

Gout Flares

Prophylaxis for gout flares was provided for 6-months in the CONFIRMS Study. The percentages of subjects who required treatment for gout flares (Day 1 through Month 6) were 31%, 31%, and 25% for the febuxostat 40 mg, febuxostat 80 mg, and allopurinol groups, respectively. The differences between both febuxostat treatment groups and allopurinol were statistically significant. Subjects in the CONFIRMS Study who had completed one of the febuxostat long-term studies (FOCUS and EXCEL) had fewer gout flares (3% across treatment groups) than subjects who had not completed one of these studies (33%) (Figure 6).

Figure 6 Gout Flare Rate by Time Interval (CONFIRMS Study)



Interval (wk)	1-4	4-8	8-12	12-16	16-20	20-24	24-28
Feb 40 mg[a]	746	723	712	681	672	646	630
Feb 80 mg[a]	738	709	695	657	643	616	603
Allopurinol[a]	743	717	691	664	656	633	620

a Sample size at each time interval.

7.2.6 Comparison and Analyses of Efficacy Results Across Controlled Studies

7.2.6.1 Reductions in sUA Levels

Comparisons of changes in sUA levels across studies are discussed in this section; comparisons across studies in reduction of gout flares and resolution of tophi, which occur with longer duration of treatment, are discussed in Section 7.2.8 with results from the open-label, long-term extension study.

The reproducibility of the effect of febuxostat on sUA levels is shown in Table 17. The four controlled studies had varying treatment periods, ranging from 4 weeks to 52 weeks, but all demonstrate the effectiveness of febuxostat in lowering sUA levels to <6.0 mg/dL in the majority of subjects. Although there were differences in the definition of responders in the studies (sUA <6.0 mg/dL at the last 3 measurements versus the Final Visit), when these definitions are aligned, febuxostat's efficacy was clearly replicated across all studies.

Table 17 Proportion of Subjects With sUA Levels <6.0 mg/dL at the Final Visit (Phase 2 and 3 Controlled Studies)

Study	Duration of Treatment	Placebo	Febuxostat 40 mg	Febuxostat 80 mg	Allopurinol 300 mg[a]
CONFIRMS	6 months	NE	45%[d] (342/757)	67%[b,c] (507/756)	42% (318/755)
APEX	28 weeks	1% (1/127)	NE	72%[b,e] (183/253)	39%[e] (102/263)
FACT	52 weeks	NE	NE	74%[b] (185/249)	36% (88/242)
Dose-Ranging	4 weeks	0% (0/35)	56%[e] (19/34)	76%[e] (28/37)	NE

NE = treatment/dose not evaluated.

a In CONFIRMS, 145 allopurinol subjects were dosed at 200 mg. In APEX, 10 allopurinol subjects were dosed at 100 mg.

b Indicates statistical significance versus allopurinol at $p<0.001$.

c Indicates statistical significance versus febuxostat 40 mg at $p<0.001$.

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

e Indicates statistical significance versus placebo at $p<0.001$.

7.2.6.2 Subgroup Analysis of sUA Levels

Subgroups of the gout population of special interest are patients with more severe disease and patients with impaired renal function. Efficacy data were analyzed by subgroup for baseline sUA level (≥10 mg/dL), tophi (yes; no), and renal function (≥90 mL/min; 60-89 mL/min; >30-59 mL/min). Discussion of the subgroup results will focus on the febuxostat recommended doses of 40 mg and 80 mg in comparison with allopurinol.

7.2.6.2.1 Baseline sUA ≥10 mg/dL

The treatment goal of sUA <6.0 mg/dL is more difficult to achieve in subjects with very high baseline sUA levels. Approximately one-third of subjects enrolled in the Phase 3 controlled studies had a sUA level ≥10 mg/dL (39% in APEX; 41% in FACT; and 32% in CONFIRMS). The response rates for subjects with baseline sUA ≥10.0 mg/dL, and for the overall subject population for comparison, are shown by study and treatment in Table 18. People with higher baseline sUA levels had lower response rates regardless of treatment. Febuxostat 80 mg was more effective in those subjects than febuxostat 40 mg and allopurinol.

Table 18 Proportion of Subjects With Baseline sUA ≥10 mg/dL With Final Visit sUA Level <6.0 mg/dL (Phase 3 Controlled Studies)

Study	Febuxostat 40 mg % (n/N)	Febuxostat 80 mg % (n/N)	Allopurinol % (n/N)
Subjects With Baseline sUA ≥10 mg/dL			
APEX	NE	60 (62/103)[a]	21 (19/89)
FACT	NE	67 (70/104)[a]	21 (22/103)
CONFIRMS	27 (66/249)	49 (125/254)[b]	31 (72/230)
All Subjects			
APEX	NE	72 (183/253)[a]	39 (102/263)
FACT	NE	74 (185/249)[a]	36 (88/242)
CONFIRMS	45 (342/757)	67 (507/756)[b]	42 (318/755)

NE = treatment/dose not evaluated.
a Statistically significantly higher (p >0.05) than allopurinol.
b Statistically significantly higher (p >0.05) than both allopurinol and febuxostat 40 mg.

7.2.6.2.2 Baseline Tophus

The presence of tophi suggests that the subject has advanced to a chronic and potentially disabling stage of hyperuricemia and gouty arthritis. In the Phase 3 controlled studies, ≥20% of subjects had a tophus at baseline.

The presence of a baseline tophus was associated with a lower response rate than the overall study population in all treatment groups (Table 19). In the CONFIRMS Study, subjects with tophi at baseline in the febuxostat 80 mg group had a higher proportion of responders at the Final Visit than those in the febuxostat 40 mg and allopurinol groups.

Table 19 Proportion of Subjects With Tophus at Baseline With Final Visit sUA Level <6.0 mg/dL (Phase 3 Controlled Studies)

STUDY	Febuxostat 40 mg % (n/N)	Febuxostat 80 mg % (n/N)	Allopurinol % (n/N)
Subjects With Tophus at Baseline			
APEX	NE	56 (24/43)[a]	35 (22/63)
FACT	NE	67 (35/52)[a]	30 (14/46)
CONFIRM	35 (58/166)	57 (93/163)[b]	32 (47/148)
All Subjects			
APEX	NE	72 (183/253)[a]	39 (102/263)
FACT	NE	74 (185/249)[a]	36 (88/242)
CONFIRMS	45 (342/757)	67 (507/756)[b]	42 (318/755)

NE = treatment/dose not evaluated.
a Statistically significantly higher (p> 0.05) than allopurinol.
b Statistically significantly higher (p> 0.05) than both allopurinol and febuxostat 40 mg.

7.2.6.2.3 Renal Function

The allopurinol label contains recommendations for dose reduction in patients with renal impairment.[68] These reductions frequently result in failure to achieve the urate-lowering goal.[14]

Efficacy in the subgroup of subjects with mild-to-moderate renal impairment was a prespecified secondary efficacy endpoint in the CONFIRMS Study. Therefore this section focuses on results from the CONFIRMS Study. Results are also provided from a retrospective analysis for febuxostat 80 mg and allopurinol from the APEX and FACT Studies using the definitions aligned with the CONFIRMS analysis plan (see Section 6.2 in the description of the CONFIRMS Study design).

The CONFIRMS Study protocol prespecified a subgroup analysis for subjects with mild-to-moderate renal impairment. Comparing subjects with mild or moderate renal impairment, statistically significantly more subjects receiving febuxostat 80 mg (72%) and febuxostat 40 mg (50%) achieved the target sUA level <6.0 mg/dL compared to subjects receiving allopurinol (42%) in CONFIRMS. These results were comparable to those seen in the APEX and FACT Studies with febuxostat 80 mg in subjects with mild or moderate renal impairment (78% and 77% achieved sUA <6.0 mg/dL, respectively, compared to 43% and 45% of those subjects in the allopurinol groups).

The renal impaired subgroups were further evaluated separating subjects with mild impairment from those with moderate renal impairment, so differences were explored between subjects with normal function, mild impairment, and moderate impairment. For all 3 categories of renal function, response rates were statistically significantly greater in the febuxostat 80 mg group compared to febuxostat 40 mg and allopurinol groups (Table 20).

Table 20 Proportion of Subjects With sUA <6.0 mg/dL at Final Visit by Baseline Renal Status (CONFIRMS Study)

Baseline Renal Function	Febuxostat 40 mg (N=757) % (n/N)	Febuxostat 80 mg (N=756) % (n/N)	Allopurinol (N=755) % (n/N)
Normal (≥90 mL/min)	37 (104/278)	58 (147/253)[a]	42 (106/254)
Mild Impairment (60-89 mL/min)	52 (182/349)	72 (263/367)[a]	46 (169/365)
Moderate Impairment (30-59 mL/min)	43 (56/130)	71 (97/136)[a]	32 (43/136)[b]

a Statistically significantly ($p<0.05$) higher than both allopurinol and febuxostat 40 mg.
b All subjects in the allopurinol group with moderate impairment received 200 mg.

The APEX and FACT Studies showed similar response rates in the febuxostat 80 mg group for subjects with renal impairment as were seen in the CONFIRMS Study (Table 21 and Table 22). Response rates remained statistically significantly greater in the febuxostat 80 mg group compared to the allopurinol group for all 3 categories of renal function (normal, mild, moderate).

Table 21 Proportion of Subjects With sUA <6.0 mg/dL at Final Visit by Baseline Renal Status - ITT Subjects (APEX Study)

Baseline Renal Function	Febuxostat 80 mg % (n/N)	Allopurinol % (n/N)
Normal (≥90 mL/min)	67 (85/127)[a]	34 (44/128)
Mild Impairment (>60-89 mL/min)	82 (78/95)[a]	45 (43/95)
Moderate Impairment (<60 mL/min)	65 (20/31)[a]	38 (15/40)[b]

a Statistically significantly ($p<0.05$) higher than allopurinol.
b Ten subjects who had creatinine ≥1.5 to <2.0 mg/dL and received 100 mg are included in the moderate impairment group; those subjects had 0% response rate.

Table 22 Proportion of Subjects With sUA <6.0 mg/dL at Final Visit by Baseline Renal Status - ITT Subjects (FACT Study)

Baseline Renal Function	Febuxostat 80 mg % (n/N)	Allopurinol % (n/N)
Normal (≥90 mL/min)	72 (87/121)[a]	28 (34/121)
Mild Impairment (>60-89 mL/min)	73 (74/102)[a]	40 (37/92)
Moderate Impairment (<60 mL/min)	92 (24/26)[a]	59 (17/29)

a Statistically significantly ($p<0.05$) higher than allopurinol.

7.2.7 Open-Label, Long-Term Extension Studies

Gout is a chronic disease. The open-label, long-term extension studies were designed to evaluate the safety of taking febuxostat over an extended period. Efficacy measurements (sUA, gout flare, and tophi resolution) were also included in the studies. However, because the study design allowed subjects to be switched between treatments as needed (see description of study design in Section 6.2), comparisons across treatments are confounded and limit the usefulness of by-treatment comparisons. The efficacy endpoints of the open-label, long-term extension studies were provided in Table 3.

7.2.7.1 Statistical Methodology - Open-Label, Long-Term Extension Studies

In the open-label, long-term extension studies, subjects could be switched to another treatment based on the subject's sUA level, an AE, or at the investigator's discretion. The number of subjects was much smaller and the treatment duration much shorter in the allopurinol group than in the febuxostat 80 mg and 120 mg groups due to study design and treatment switches. To account for the possibility of treatment switches, one of the following two methods was used to define treatment group.

Final Stable Treatment summarized subjects by the drug and/or dose that the subject was receiving after no further dose changes were made. The duration of the Final Stable Treatment was the number of days between the first day of a subject's final dose and the last day of study drug in the study.

Treatment at Observation summarized subjects by the treatment they were receiving at the time of an observation. For analyses by Treatment at Observation, the denominator for a

treatment was all subjects exposed to the treatment for the time interval of interest. Since subjects may have received more than one treatment, some subjects may have been included in more than one treatment group during the time interval. For example, a subject initially assigned to febuxostat 80 mg who subsequently changed dose to febuxostat 120 mg was included in both febuxostat doses for the purpose of defining the "N" for that time period.

Final stable treatment was used to summarize gout flare and tophi data while treatment at observation was used to summarize sUA results.

7.2.7.2 FOCUS Study - Efficacy Results

The FOCUS Study was an open-label, multicenter study designed for subjects who previously completed four weeks of treatment with febuxostat or placebo in the double-blind, controlled Phase 2 Dose-Ranging Study. The data from Day 28 in that study were considered to be Day 1 data for the FOCUS Study and Baseline data from the Phase 2 Dose-Ranging Study was used as the baseline data for the FOCUS Study.

The majority of subjects required no dose adjustments and stayed on the initial dose of febuxostat 80 mg (Table 23). Most dose adjustments were to maintain sUA levels, per protocol, between 3.0 and 6.0 mg/dL.

Subject Disposition

Fifty-eight (50%) subjects discontinued the study; 38 (33%) subjects discontinued within the first year (Table 24). The most frequently reported primary reason for discontinuation was personal reasons.

Table 23 Dose Adjustments to Achieve Final Stable Dose (FOCUS Study)

Adjustment	All Subjects (N=116) n (%)
No Adjustments	72 (62)
One Adjustment	32 (28)
From 80 mg to 40 mg	4 (3)
From 80 mg to 120 mg	28 (24)
Two Adjustments	11 (9)
From 80 mg to 40 mg to 80 mg	3 (3)
From 80 mg to 120 mg to 40 mg	4 (3)
From 80 mg to 120 mg to 80 mg	4 (3)
Multiple Adjustments	1 (1)
From 80 mg to 120 mg to 80 mg to 40 mg to 80 mg to 120 mg	1 (1)

Table 24 Timing and Reasons for Discontinuation (FOCUS Study)

	Final Stable Dose[a]			
	Febuxostat 40 mg n (%)	Febuxostat 80 mg n (%)	Febuxostat 120 mg n (%)	All Subjects n (%)
Subjects Enrolled	8	79	29	116
Subjects Who Discontinued	2 (25)	38 (48)	18 (62)	58 (50)
Timing of Discontinuation				
Year 1	2 (25)	23 (29)	13 (45)	38 (33)
≤1 Month	0	7 (9)	0	7 (6)
1-2 Months	0	7 (9)	2 (7)	9 (8)
2-3 Months	0	1 (1)	2 (7)	3 (3)
3-6 Months	0	2 (3)	6 (21)	8 (7)
6-12 Months	2 (25)	6 (8)	3 (10)	11 (10)
Year 2	0	5 (6)	2 (7)	7 (6)
Year 3	0	4 (5)	1 (3)	5 (4)
Year 4	0	5 (6)	1 (3)	6 (5)
Year 5	0	1 (1)	0	1 (1)
Year 6	0	0	1 (3)	1 (1)
Primary Reason for Discontinuation				
Personal Reason(s)	0	14 (18)	8 (28)	22 (19)
Adverse Event	1 (13)	10 (13)	2 (7)	13 (11)
Other[b]	1 (13)	6 (8)	2 (7)	9 (8)
Gout Flare	0	4 (5)	4 (14)	8 (7)
Lost to Follow-up	0	3 (4)	2 (7)	5 (4)
Protocol Violation	0	1 (1)	0	1 (1)

a Dose at the time of discontinuation.

b Other reasons for discontinuation include: unstable laboratory results, subject vacation, noncompliance, subject declined to continue participation, investigator discretion, sponsor request, uncontrolled sUA.

Serum Urate Levels

Serum urate levels <6.0 mg/dl were maintained over time. The percentage of subjects with sUA levels <6.0 mg/dL at the Final Visit was 83% (95/114). Febuxostat successfully maintained sUA levels <6.0 mg/dL at each time interval (Table 25). All doses had similar effects because the dose was adjusted to achieve sUA <6.0 mg/dL. Note that subject exposure to the 40 mg and 120 mg doses was limited due to the design of the study (8 subjects and 29 subjects, respectively).

Table 25 Percentage of Subjects With sUA Levels <6.0 mg/dL by Dose at Observation and Selected Visits (FOCUS Study)

	Febuxostat			
Visit	40 mg % (n/N)	80 mg % (n/N)	120 mg % (n/N)	Total % (n/N)
Week 28	50 (5/10)	93 (54/58)	65 (11/17)	82 (70/85)
Week 52 (Year 1)	57 (4/7)	85 (47/55)	67 (12/18)	79 (63/80)
Week 80	50 (4/8)	82 (41/50)	57 (8/14)	74 (53/72)
Week 104 (Year 2)	63 (5/8)	76 (37/49)	92 (12/13)	77 (54/70)
Week 156 (Year 3)	67 (4/6)	84 (38/45)	92 (12/13)	84 (54/64)
Week 208 (Year 4)	83 (5/6)	92 (36/39)	85 (11/13)	90 (52/58)
Week 260 (Year 5)	100 (6/6)	93 (38/41)	91 (10/11)	93 (54/58)
Final Visit[a,b]	100 (8/8)	82 (65/79)	81 (22/27)	83 (95/114)

Note: Febuxostat dose based on subject's most recent dose continuously received for at least 14 days prior to visit.

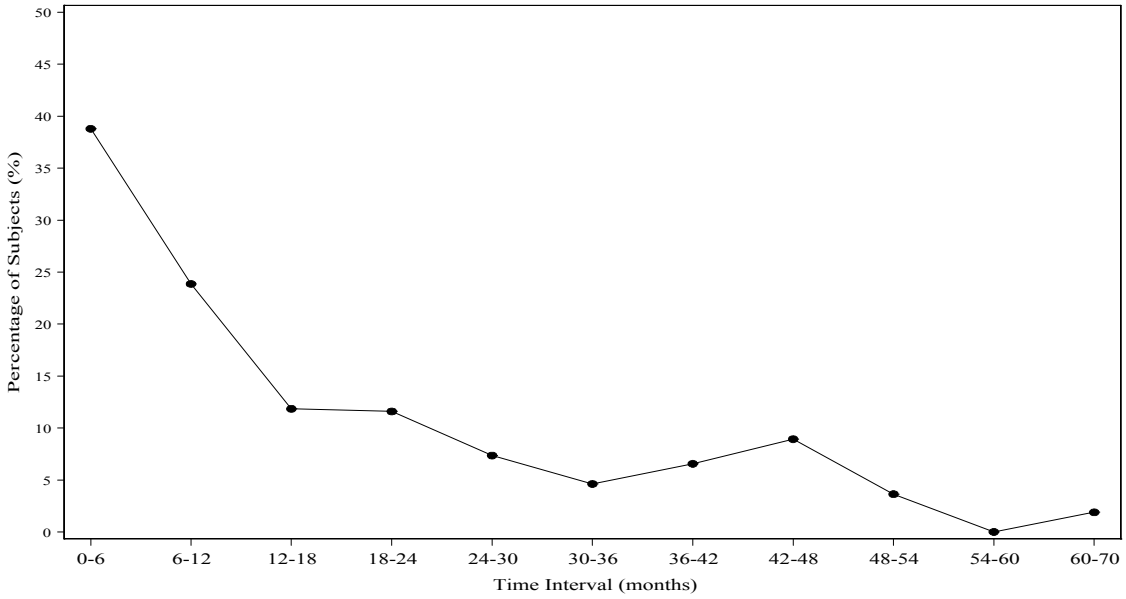
a Dose at Final Visit is the final stable dose.

b Two subjects did not have any postbaseline sUA values.

Gout Flares

Gout flare rates by 6-month intervals through Month 60 are illustrated for all doses combined in Figure 7. Since subjects were receiving prophylaxis for gout flares during the first four weeks of the study, the incidence of gout flares increased immediately after the prophylaxis period ended and then began a steady decline during the remainder of the study. The rate of decline in the incidence of gout flares is greatest during the first year of exposure, followed by a more moderate reduction in Months 14 through 50.

Figure 7 Percentages of Subjects Receiving Treatment for Gout Flares by 6-Month Intervals - All Final Stable Doses Combined (FOCUS Study)



Interval (m)	0-6	6-12	12-18	18-24	24-30	30-36	36-42	42-48	48-54	54-60	60-70
All doses[a]	116	88	76	69	68	65	61	56	55	55	53

a Sample size at each time interval.

Tophi

Of the 116 subjects enrolled in the FOCUS Study, 26 subjects had at least one palpable tophus at baseline. By their Final Visit, 69% of these subjects had resolution of that tophus (Table 26).

Table 26 Presence of Tophi at Baseline and by Visit (FOCUS Study)

Time Period	Subjects With Tophi at Baseline n	Tophus Absent n (%)
Baseline	26	--
Week 52 (Year 1)	19	3 (16)
Week 104 (Year 2)	16	8 (50)
Week 156 (Year 3)	15	10 (67)
Week 208 (Year 4)	14	11 (79)
Week 260 (Year 5)	14	9 (64)
Final Visit	26	18 (69)

Note: Baseline is the last measurement prior to the first dose of study drug. Values more than 1 day after the last dose of study drug are not included in the analysis.

7.2.7.3 EXCEL Study - Efficacy Results

Subjects who completed either the APEX or FACT Studies and continued to meet selection criteria were eligible to enroll in the EXCEL Study, a Phase 3, open-label, multicenter, randomized, long-term (up to 40 months) safety study. When the study was initiated, all subjects started on febuxostat 80 mg. The dose could then be increased to 120 mg and then subsequently decreased to 80 mg based on the subject's sUA level, an AE, or at the investigator's discretion. After an amendment was made to the protocol at FDA's request, subjects newly enrolled in the study were randomized in a 2:2:1 ratio to one of 3 treatments: febuxostat 80 mg, febuxostat 120 mg, or allopurinol (300/100 mg depending on renal function) (see details on the study design in Section 6.2).

Subjects who had 3 consecutive sUA levels >6.0 mg/dL after a change in therapy were to be withdrawn from the study and were considered treatment failures, unless the increased sUA level was due to change in diet, alcohol intake, interruption of study drug dosing, or other factors. All subjects in the study were to be on a stable drug and dose by the end of 6 months of treatment.

Study Drug Exposure

A total of 1086 subjects were enrolled in this study and received at least one dose of study drug. Of these subjects, 606, 388, and 92 subjects had final stable treatment of febuxostat 80 mg, febuxostat 120 mg, and allopurinol 300/100 mg, respectively. The reasons for treatment changes from subjects' initial treatment assignments are summarized in Table 27 for subjects enrolled both before and after the addition of the allopurinol arm. The majority of treatment changes were due to sUA levels >6.0 mg/dL. Subjects assigned to allopurinol were more likely to change treatment assignment to febuxostat than vice versa. Of the 145 subjects who initially started on allopurinol, 86 (59%) changed to febuxostat, compared to 26 (3%) of the 941 subjects who started on febuxostat and changed to allopurinol. Few subjects changed initial treatment due to adverse event.

Table 27 Summary of Reasons for Treatment Change from Initial Treatment Assignment (EXCEL Study)

Reasons for Treatment Change	Febuxostat 80 mg N=350			Febuxostat 120 mg N=1			Allopurinol		
		Changed to			Changed to			Changed to	
	n (%)	Feb 120	Allo	n (%)	Feb 80	Allo	n (%)	Feb 80	Feb 120
Subjects Who Enrolled Prior to Addition of Allopurinol Group[a]									
Total	97 (28)	96	1[a]	1 (100)	1	0	NA	NA	NA
sUA >6.0 mg/dL	87 (25)	87	0	0	0	0	NA	NA	NA
sUA <3.0 mg/dL	1 (<1)	0	1	1 (100)	1	0	NA	NA	NA
Adverse Event	0	0	0	0	0	0	NA	NA	NA
Other	6 (2)	6	0	0	0	0	NA	NA	NA
No Reason Provided	3 (1)	3	0	0	0	0	NA	NA	NA
	Febuxostat 80 mg N=299			**Febuxostat 120 mg N=291**			**Allopurinol N=145**		
		Changed to			Changed to			Changed to	
Reasons for Treatment Change	**n (%)**	**Feb 120**	**Allo**	**n (%)**	**Feb 80**	**Allo**	**n (%)**	**Feb 80**	**Feb 120**
Subjects Who Enrolled After Addition of Allopurinol Group[b]									
Total	67 (22)	66	1	90 (31)	66	24	86 (59)	85	1
sUA >6.0 mg/dL	54 (18)	54	0	22 (8)	0	22	82 (57)	81	1
sUA <3.0 mg/dL	0	0	0	40 (14)	40	0	0	0	0
Adverse Event	1 (<1)	0	1	7 (2)	6	1	1 (1)	1	0
Other	12 (4)	12	0	20 (7)	19	1	3 (2)	3	0
No Reason Provided	0	0	0	1 (<1)	1	0	0	0	0

Feb 80 = febuxostat 80 mg; Feb 120 = febuxostat 120 mg; Allo = allopurinol; NA = not applicable.

a Prior to protocol amendment, all subjects were to be initially treated with febuxostat 80 mg QD and were not to be changed to allopurinol. However, one subject switched to allopurinol before the allopurinol group was added to the study design.

b A protocol amendment caused the subjects to be randomized to one of the three treatments. Subjects were eligible to change to any of the three treatments.

Subject Disposition

Four hundred and twenty-two (39%) subjects discontinued the study; 196 (18%) subjects discontinued within the first year (Table 28). A significantly higher proportion of subjects in the allopurinol group than the febuxostat 80 mg and 120 mg groups discontinued the study due to therapeutic failure.

Table 28 Timing and Reasons for Discontinuation (EXCEL Study)

Disposition	Final Stable Treatment			All Subjects n (%)
	Febuxostat 80 mg n (%)	Febuxostat 120 mg n (%)	Allopurinol n (%)	
Enrolled	606	388	92	1086
Discontinued	194 (32)	171 (44)	57 (62)	422 (39)
Timing of Discontinuation				
Year 1	78 (13)	86 (22)	32 (35)	196 (18)
≤1 Month	11 (2)	9 (2)	3 (3)	23 (2)
1-2 Months	11 (2)	3 (1)	3 (3)	17 (2)
2-3 Months	5 (1)	7 (2)	3 (3)	15 (1)
3-6 Months	18 (3)	15 (4)	4 (4)	37 (3)
6-12 Months	33 (5)	52 (13)	19 (21)	104 (10)
Year 2	75 (12)	55 (14)	15 (16)	145 (13)
Year 3	41 (7)	30 (8)	10 (11)	81 (8)
Primary Reason for Discontinuation				
Did Not Continue Under Amendment Extending Study[a]	1 (<1)	1 (<1)	2 (2)	4 (<1)
Adverse Event	54 (9)	22 (6)	2 (2)	78 (7)
Protocol Violation	6 (1)	3 (1)	3 (3)	12 (1)
Personal Reason(s)	39 (6)	31 (8)	8 (9)	78 (7)
Lost to Follow-up	42 (7)	39 (10)	9 (10)	90 (8)
Therapeutic Failure	10 (2)	38 (10)	22 (24)	70 (6)
Gout Flare	2 (<1)	3 (1)	0	5 (1)
Other	40 (7)	34 (9)	11 (12)	85 (8)

a With a protocol amendment, the study duration was extended from March 2006 to December 2006.

Serum Urate Levels

Since subjects had completed the APEX and FACT Studies, the majority (~60%) of subjects entering the EXCEL Study had sUA levels <6.0 mg/dL at enrollment (Table 29). At the final visit on treatment, 53% of subjects on allopurinol had sUA levels <6.0 mg/dL, which was more than 20 percentage points lower than either febuxostat treatment (83% and 75% in subjects taking 80 mg and 120 mg, respectively).

Table 29 Percentage of Subjects With Serum Urate Levels <6.0 mg/dL by Study Treatment at Observation (EXCEL Study)

Visit (End of Month)	Febuxostat 80 mg (N=801) % (n/N)	Febuxostat 120 mg (N=487) % (n/N)	Allopurinol (N=178) % (n/N)
Day 1[a]	64 (403/631)	60 (171/286)	62 (85/137)
Month 1	81 (500/619)	87 (242/278)	46 (64/139)
Month 6	84 (475/564)	77 (259/336)	60 (52/87)
Month 12	88 (457/520)	79 (238/302)	75 (46/61)
Month 24	89 (404/455)	84 (202/242)	75 (36/48)
Month 36	89 (130/146)	87 (74/85)	82 (9/11)
Last Visit on Treatment	83 (496/596)	75 (283/379)	53 (47/88)

a Day 1 is the last value from the previous study (APEX or FACT).

The last visit on treatment most accurately reflects the effect of allopurinol on sUA levels. Treatments were to be stabilized by Month 6 and maintained for the remainder of the study. Therefore, the responder rates were higher over time because subjects not achieving goal on stable treatment were discontinued per protocol.

Gout Flares

During the first year of treatment on either dose of febuxostat, the incidence of gout flares was greater than the incidence during all subsequent years combined (Table 30). Gout flare rates were reduced to almost zero in all 3 final treatment groups. This was expected, as per protocol, only subjects who achieved and maintained sUA levels of <6.0 mg/dL were to continue on treatment.

Table 30 Incidences of Gout Flares Requiring Treatment (EXCEL Study)

Time Interval	Febuxostat 80 mg % (n/N)	Febuxostat 120 mg % (n/N)	Allopurinol % (n/N)
By Final Stable Treatment			
Overall	34.5 (209/606)	47.2 (183/388)	32.6 (30/92)
≤1 to 6 Months	23.9 (145/606)	38.1 (148/388)	25.0 (23/92)
>6 to 12 Months	15.4 (85/552)	19.0 (63/332)	18.6 (13/70)
>12 to 18 Months	9.3 (48/516)	13.7 (40/293)	16.1 (9/56)
>18 to 24 Months	7.0 (34/483)	5.6 (15/266)	10.4 (5/48)
>24 to 30 Months	3.2 (14/439)	3.4 (8/234)	4.5 (2/44)
>30 to 36 Months	1.8 (7/392)	3.6 (7/193)	2.7 (1/37)
>36 to 42 Months	1.2 (2/170)	0 (0/10)	0 (0/1)
≤1 Year	29.4 (178/606)	42.5 (165/388)	28.3 (26/92)
>1 Year	15.3 (79/516)	19.8 (58/293)	23.2 (13/56)

Note: The numerator (n) is the number of subjects with a gout flare in the time interval. The denominator (N) is the number of subjects exposed to at least one dose of that treatment in the time interval being summarized. Subjects who reported 2 or more gout flares were counted only once in each time interval.

Tophi

Of the 1086 subjects enrolled in the EXCEL Study, 214 (20%) subjects had tophi at the time of enrollment. The resolution of the primary tophi is presented at 6-month intervals by final stable treatment in Table 31. Day 1 values show the level of tophi resolution that occurred in APEX or FACT before the subject entered the EXCEL Study. For subjects on either febuxostat dose, approximately 40% of subjects had tophus resolution after 18 months of treatment.

Table 31 Subjects With Resolution of Primary Palpable Tophus by Selected Study Visits: Final Stable Treatment (EXCEL Study)

Scheduled Visit	Febuxostat 80 mg		Febuxostat 120 mg		Allopurinol	
	N	100% Reduction From Baseline n (%)	N	100% Reduction From Baseline n (%)	N	100% Reduction From Baseline n (%)
Day 1[a]	88	23 (26)	34	8 (24)	10	3 (30)
Month 6	85	32 (38)	57	8 (14)	9	4 (44)
Month 12	80	30 (38)	51	17 (33)	9	3 (33)
Month 18	73	35 (48)	48	19 (40)	9	3 (33)
Month 24	64	32 (50)	32	12 (38)	4	1 (25)
Month 30	20	6 (30)	15	7 (47)	0	N/A
Month 36	1	0	0	N/A	0	N/A
Final Visit	107	49 (46)	76	27 (36)	14	4 (29)

N/A = not available
Note: Baseline is defined as the last examination prior to the first dose of study drug in the APEX and FACT.
a Day 1 is the last value from the previous study (APEX or FACT Study).

7.2.8 Effect of sUA Reduction on Clinical Outcomes

7.2.8.1 Gout Flares

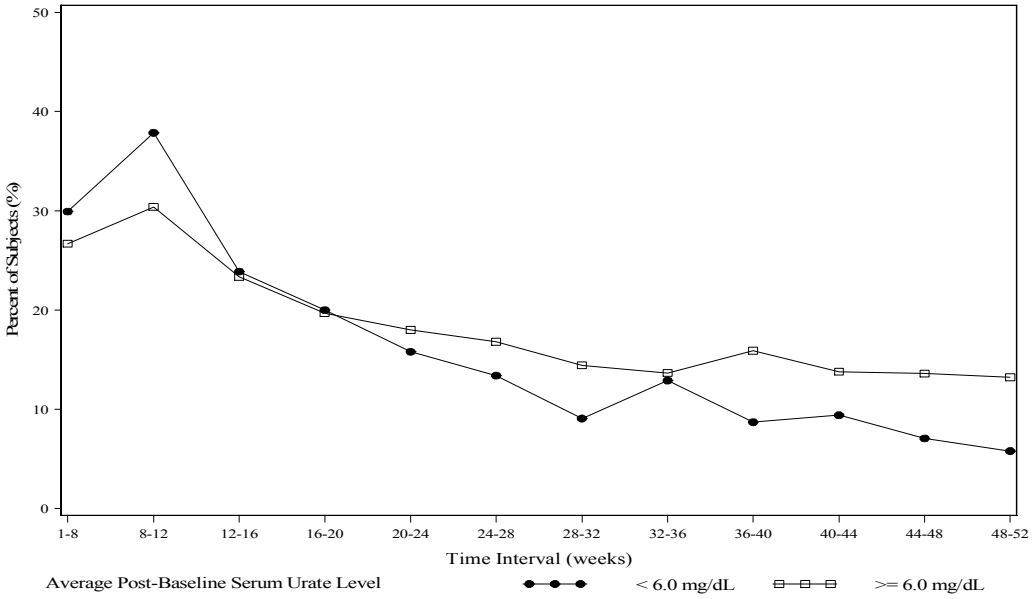
The initiation of ULT (with any active agent) is accompanied by a transiently increased risk for acute gout flares. Borstad and colleagues reported that 77% of subjects experienced an acute gout flare in the first 6 months of allopurinol therapy.[40] A comparison of the percentages of subjects who required treatment for gout flares between the APEX Study with 8 weeks of prophylaxis and the CONFIRMS Study with 6 months of prophylaxis, demonstrated that prophylactic treatment may be beneficial for a duration of up to 6 months.

The relationship between reduction in sUA and gout flares was explored by average sUA level during the controlled studies and for longer term use of febuxostat during the extension studies. The analysis of the controlled studies was performed using the FACT and APEX data that grouped subjects by their average postbaseline sUA level regardless of treatment. (The CONFIRMS Study was not included because it required prophylaxis for the entire duration of study treatment.)

The proportion of subjects requiring treatment for a gout flare in APEX and FACT was lower for subjects with sUA <6.0 mg/dL than for subjects with sUA ≥6.0 mg/dL (Figure 8). At Week 48-52, the proportion of subjects requiring treatment for a gout flare was statistically

significantly lower in subjects with sUA <6.0 mg/dL compared to subjects with sUA ≥6.0 mg/dL (6% vs. 13%).

Figure 8 **Percent of Subjects Requiring Treatment for a Gout Flare by Time Interval and Average Postbaseline sUA Level (<6.0 and ≥6.0 mg/dL) (Combined APEX and FACT Studies)**

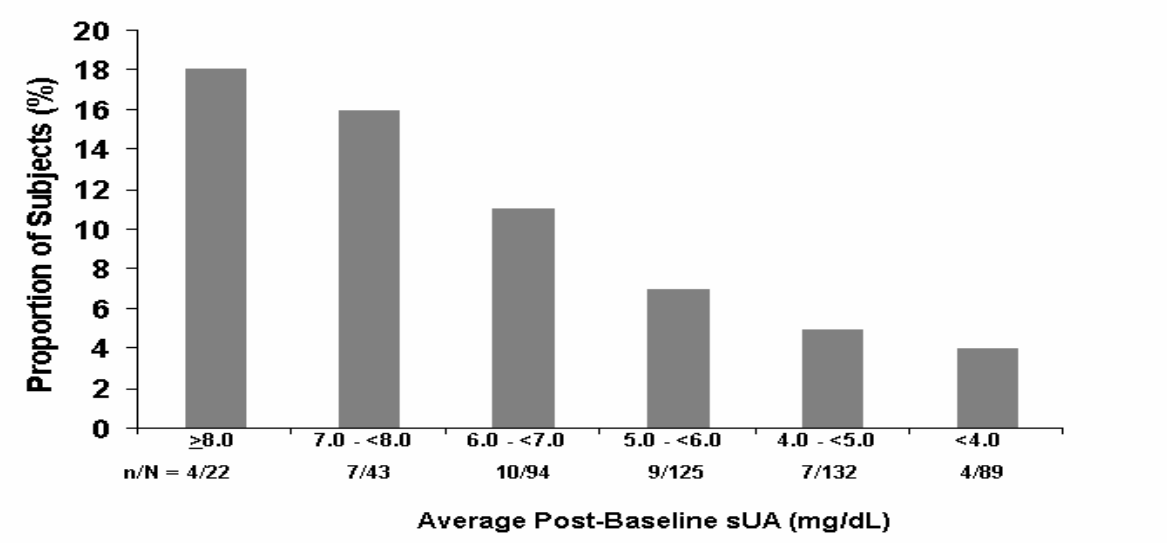


Interval (wk)	1-8	8-12	12-16	16-20	20-24	24-28	28-32	32-36	36-40	40-44	44-48	48-52
sUA <6.0[a]	1126	1022	972	930	893	874	618	380[b]	368	362	354	346
sUA ≥6.0[a]	641	579	544	518	500	488	333	176[b]	170	167	162	159

a Sample size at each time interval.
b The APEX Study was a 28-week study; data after 28 weeks are for subjects in the FACT Study only.

This relationship between gout flares and sUA level was further explored with a more in-depth breakdown of sUA levels from the 52-week FACT Study. Subjects with lower average postbaseline sUA levels had fewer flares by the end of one year of treatment (Weeks 48 to 52) compared to subjects with higher average postbaseline sUA levels, and the frequency of gout flares decreased in direct proportion to postbaseline sUA level, as shown in Figure 9.

Figure 9 **Proportion of Subjects Requiring Treatment for Gout Flare at the End of One Year of Treatment By Average Postbaseline sUA (FACT Study)**



The influence of potential factors contributing to the likelihood of experiencing a gout flare was explored via a multivariate logistic regression model for the proportion of subjects requiring treatment for a gout flare. Separate models were created for flares between Weeks 24 and 28 and between Weeks 48 and 52. The factors included in the model were treatment group, baseline serum urate level, average postbaseline serum urate level, average postbaseline percent change in serum urate level, and presence of a baseline tophus.

The likelihood of experiencing a gout flare increased with greater changes in sUA level but decreased with lower average postbaseline sUA levels (Table 32). A patient's disease burden, as evidenced by the presence of palpable tophi, also increased the likelihood of experiencing a gout flare, but this effect was only statistically significant between Weeks 24 and 28. The factors of treatment group and baseline serum urate level were not statistically significant in the model.

Table 32 Multivariate Logistic Regression Models of Proportion of Subjects Requiring Treatment for a Gout Flare (Combined APEX and FACT Studies)

Timepoint Effect	Estimated Adjusted Odds Ratio	95% CI for Odds Ratio	Effect P-value
Week 24 to Week 28 (Model p-value=0.0003)			
Average Postbaseline Serum Urate Level	1.418	(1.161, 1.731)	0.0006
Average Postbaseline Percent Change in Serum Urate Level	0.971	(0.951, 0.991)	0.0048
Baseline Palpable Tophus Presence (Tophus Present vs Tophus Absent)	1.464	(1.027, 2.086)	0.0353
Week 48 to Week 52 (Model p-value <0.0001)			
Average Postbaseline Serum Urate Level	2.695	(1.723, 4.215)	<0.0001
Average Postbaseline Percent Change in Serum Urate Level	0.921	(0.876, 0.968)	0.0012
Baseline Palpable Tophus Presence	1.591	(0.762, 3.321)	0.2160

CI = confidence interval.
Note: A multivariate logistic regression model was fit to the proportion of subjects requiring treatment for a gout flare at each timepoint.

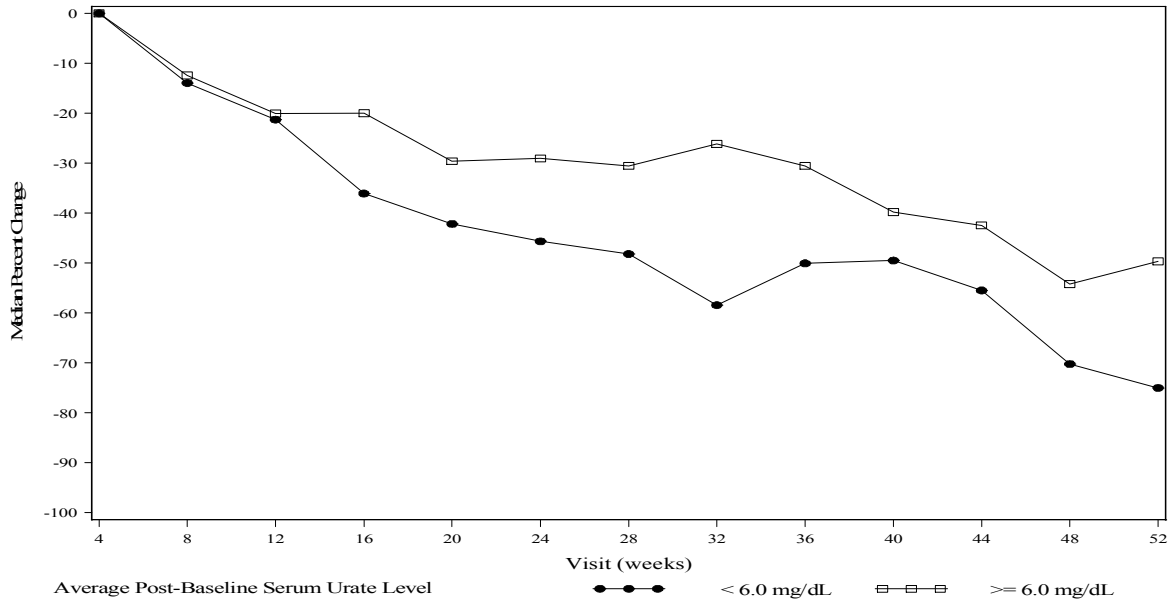
The clinical benefit of reducing gout flares by lowering sUA becomes most apparent after long-term treatment with ULT, as many studies have previously shown.[10,11,21,31,42,69] The reduction in gout flares observed in the 52-week FACT Study is supported by the reduction observed in the open-label, long-term extension FOCUS and EXCEL Studies. With long-term use (up to 5 years) in the FOCUS Study, the percentages of subjects who experienced gout flares dropped from 39% during the first 6 months to <10% after approximately 24 months, <4% after approximately 48 months, and to almost zero at the end of the study. The EXCEL Study included subjects with up to 40 months of exposure, and similar to the FOCUS Study, a continuous decrease in the incidence of gout flares was observed in subjects with an sUA level of <6.0 mg/dL.

7.2.8.2 Tophus Size Reduction and/or Resolution

In the combined data from APEX and FACT, the median percent change from baseline in primary tophus size was plotted versus time, separately for subjects with an average postbaseline serum urate level ≥6.0 mg/dL and <6.0 mg/dL across all treatment groups (Figure 10). Tophi were not assessed after baseline for the CONFIRMS and Dose-Ranging Studies.

The median percent change from baseline in primary tophus size was numerically greater in the group that achieved an average postbaseline sUA level <6.0 mg/dL compared to the group that achieved an average postbaseline serum urate level ≥6.0 mg/dL by Week 16 and the response was maintained throughout the rest of treatment.

Figure 10 **Median Percent Change From Baseline in Primary Tophus Size by Average Postbaseline sUA Level (<6.0 and ≥6.0 mg/dL) - Subjects With a Primary Tophus at Baseline (Combined APEX and FACT Studies)**



Week	4	8	12	16	20	24	28	32	36	40	44	48	52
sUA <6.0[a]	182	180	165	152	142	142	138	60[b]	52	54	56	56	54
sUA ≥6.0[a]	142	124	124	111	109	106	101	39[b]	37	36	35	34	34

a Sample size at each time interval.
b The APEX Study was a 28-week study; data after 28 weeks are for subjects in the FACT Study only.

For subjects who had a tophus at baseline in long-term studies (FOCUS and EXCEL Studies), sustained sUA level reductions of <6.0 mg/dL showed a clear clinical outcomes benefit in the reduction in size of the primary palpable tophus. See Section 7.2.7.2 and Section 7.2.7.3 for tophi results in the FOCUS and EXCEL Studies, respectively.

7.3 Efficacy Conclusions

Subjects in the febuxostat clinical program were representative of the general gout population for which febuxostat use is intended. Febuxostat at all doses is effective in treating hyperuricemia in patients with gout. The clinical benefits of reducing and maintaining sUA levels <6.0 mg/dL over time result in reduced gout flares and size and presence of tophi. Febuxostat 80 mg is superior to febuxostat 40 mg and allopurinol in its ability to lower sUA to <6.0 mg/dL. Subjects with tophi or sUA levels ≥10.0 mg/dL would benefit from febuxostat 80 mg. Febuxostat at both doses is more effective than allopurinol in gout patients with mild-to-moderate renal impairment. Febuxostat, at doses of 40 mg and 80 mg, is a treatment option that could provide improved efficacy for gout patients.

8 Clinical Safety

8.1 Safety Overview

Febuxostat was well tolerated in the clinical studies, which enrolled subjects representative of the gout and hyperuricemic population. The development program for febuxostat included 4072 subjects who received at least one dose of febuxostat, with doses ranging from 10 mg to 300 mg. Of those, 2757 subjects received febuxostat 40 mg or 80 mg in Phase 2 and Phase 3 studies.

Febuxostat has a well-characterized safety profile, which is based on the following data:

- The incidence of treatment-emergent AEs in the Phase 3 controlled studies were comparable in the febuxostat 40 mg (57%), febuxostat 80 mg (62%), and allopurinol (66%) groups. The most frequent AEs were upper respiratory tract infections, musculoskeletal and connective tissue signs and symptoms, and diarrhea.
- Febuxostat was well-tolerated during long-term treatment (up to 5 years). The incidence of AEs did not increase over time and similar types of AEs occurred with long-term use. The most frequently reported AE in all treatment groups was upper respiratory tract infections.

- Deaths occurred at similar rates in febuxostat- and allopurinol-treated subjects in the Phase 3 controlled studies (0.22% vs 0.23%). Ten deaths occurred during the open-label, long-term studies for a rate of 0.38 deaths/100 PY, which was similar to the rate of 0.45 deaths/100 PY for febuxostat during the Phase 3 controlled studies. There was no discernible pattern with respect to treatment duration or time of death.
- Adjudicated APTC events were experienced by a small number of subjects across treatment groups in the Phase 3 controlled studies.
  - In the CONFIRMS Study, which included a prospective evaluation of CV events, no APTC events were observed in the 40 mg group. The febuxostat 80 mg and allopurinol groups had the same rate (0.4%) of APTC events.
  - In the combined Phase 3 controlled studies, adjudicated APTC events were experienced by a small number of subjects across treatment groups. The rate of APTC events in the febuxostat 40 mg, febuxostat 80 mg, and allopurinol groups were 0%, 0.55%, and 0.31%. For all febuxostat-treated subjects combined, the incidence rate of APTC events was 0.37%.
- Non-APTC CV events in the combined Phase 3 controlled studies occurred in similar rates across the febuxostat 40 mg, febuxostat 80 mg, and allopurinol groups.
- In the open-label long-term extension studies, the rates of adjudicated APTC and non-APTC CV events were low and did not increase over time.
- Hepatic transaminase elevations with febuxostat were generally mild and both extent and incidence were similar to those noted with allopurinol. In the Phase 3 controlled studies, mild transaminase elevations greater than 3 times upper limit of normal (xULN) were observed (AST: 2%, 2%, and ALT: 3%, 2% in febuxostat and allopurinol groups, respectively). A few subjects experienced ALT or AST elevations ≥5xULN and they were distributed across the treatment groups. No Hy's Law or serious drug-induced liver injury occurred during the studies.

- Febuxostat was well tolerated by subjects with renal impairment. There was a small increase in AEs across all treatment groups, including allopurinol, in subjects with moderate renal impairment (CrCl 30-59 mL/min) compared to subjects with normal renal function (CrCl ≥90 mL/min) or mild renal impairment (CrCl 60-89 mL/min). Results from the controlled studies support the observations from Phase 1 studies that a dose adjustment is not necessary for patients with mild or moderate renal impairment.
- The majority of dermatologic events were mild to moderate in severity and not considered related to study drug. No life-threatening, serious cutaneous adverse reaction, such as Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis, was associated with febuxostat. One allopurinol-treated subject experienced a serious episode identified as an allopurinol hypersensitivity syndrome (AHS).

8.2 Statistical Methodology for Safety

The Phase 2 and 3 controlled studies and the open-label, long-term extension studies from the febuxostat development program that were included in the safety review were described earlier in Table 3 and Section 6.2.

Safety data from the short term (28-day) Phase 2 Dose-Ranging Study are discussed separately in Section 8.6.2.

The safety population included all subjects who received at least 1 dose of study drug. For all analyses, the allopurinol doses are combined, with the actual dose specified where applicable. Overall AEs, serious AEs (SAEs), and discontinuations due to AEs are presented for the individual studies. Integrated safety analyses were performed for 2 study groups: the combined data from the Phase 3 controlled studies (APEX, FACT, and CONFIRMS) and from the open-label, long-term extension studies (FOCUS and EXCEL).

Phase 3 Controlled Studies

For the 3 Phase 3 controlled studies (APEX, FACT, and CONFIRMS), the integrated data included 6 treatment groups: placebo, febuxostat 40 mg, 80 mg, 120 mg, 240 mg, and allopurinol. The CONFIRMS Study was completed most recently and included 3 treatment

groups: febuxostat 40 mg, febuxostat 80 mg, and allopurinol 300/200 mg. Safety data for all febuxostat doses will be presented, with discussion focusing primarily on the doses of 40 mg and 80 mg, with the higher febuxostat doses (120 mg and 240 mg) discussed when informative.

Open-Label, Long-Term Extension Studies

In the 2 open-label, long-term extension studies (FOCUS and EXCEL), the integrated data included 4 treatment groups: febuxostat 40 mg, 80 mg, 120 mg, and allopurinol. Due to study design and changes between treatment groups (discussed in detail in Section 6.2), the number of subjects is much smaller and the treatment duration much shorter in the febuxostat 40 mg and allopurinol treatment groups than in the febuxostat 80 mg and 120 mg treatment groups. In order to adjust for these substantial differences in duration of exposure, data from the open-label, long-term extension studies are summarized by patient-years of exposure (PY).

For subjects who switched from one treatment to another, AEs were assigned to the treatment the subject was receiving at the time of onset of the AE (Time of Observation). It is important to note that a subject may have been exposed to a different treatment and/or dose prior to the onset of the current AE. Approximately 60% of the allopurinol subjects in the EXCEL Study switched to febuxostat, leaving only a small number of subjects whose final stable treatment was allopurinol.

Data from the open-label, long-term extension studies were summarized by treatment group; however, comparisons across treatment groups are not appropriate due to substantial imbalance in sample sizes, treatment duration differences, and protocol-allowed switches between treatments.

8.3 Safety in Phase 3 Controlled Studies

8.3.1 Exposure – Phase 3 Controlled Studies

In the Phase 3 controlled studies, 2690 subjects received ≥1 dose of febuxostat, 1277 subjects received ≥1 dose of allopurinol, and 134 subjects received placebo. Table 33 provides the cumulative study drug exposure by treatment and febuxostat dose. The mean duration of

treatment for the total febuxostat group was 182.8 days compared to 191.9 days for the allopurinol subjects, versus 163.3 days for placebo.

Table 33 Cumulative Exposure (Phase 3 Controlled Studies)

	Treatment Group						
		Febuxostat					Allopurinol
	Placebo	40 mg	80 mg	120 mg	240 mg	Total	All Doses
Number of Subjects (n)	134	757	1279	520	134	2690	1277
Mean Exposure (days)	163.3	165.6	184.0	213.9	147.2	182.8	191.9
Cumulative Exposure							
≥1 day	134	757	1279	520	134	2690	1277
≥7 days	132	738	1246	510	130	2624	1249
≥1 month	122	723	1191	485	117	2516	1205
≥3 months	110	680	1078	423	95	2276	1116
≥6 months	101	549	892	376	83	1900	963
≥9 months	0	0	179	160	0	339	193
≥12 months	0	0	152	135	0	287	171

Note: Studies included are APEX, FACT, and CONFIRMS.

8.3.2 Demographics and Other Baseline Characteristics – Phase 3 Controlled Studies

The baseline demographics and other characteristics of subjects in the Phase 3 controlled studies (APEX, FACT, and CONFIRMS) (Table 34) were consistent with those of gout populations reported in the literature.[1,2] More than half (63%) of subjects were overweight (BMI ≥30 kg/m^2), 59% had renal impairment (43% mild or 16% moderate renal impairment), and 36% had a baseline sUA ≥10 mg/dL. Approximately 90% of subjects had at least one CV risk factor (details are provided in the Cardiovascular Section, Section 8.3.8.1).

Table 34 Demographics and Baseline Characteristics of Subjects (Phase 3 Controlled Studies)

Variable	Placebo (N=134) n (%)	Febuxostat 40 mg (N=757) n (%)	Febuxostat 80 mg (N=1279) n (%)	Febuxostat 120 mg (N=520) n (%)	Febuxostat 240 mg (N=134) n (%)	Febuxostat Total (N=2690) n (%)	Allopurinol (N=1277) n (%)
Gender							
Male	123 (92)	722 (95)	1204 (94)	499 (96)	126 (94)	2551 (95)	1201 (94)
Race							
Asian	3 (2)	26 (3)	43 (3)	17 (3)	1 (<1)	87 (3)	49 (4)
Black or African American	9 (7)	83 (11)	140 (11)	47 (9)	13 (10)	283 (11)	118 (9)
White	108 (81)	620 (82)	1011 (79)	413 (79)	107 (80)	2151 (80)	1026 (80)
American Indian or Alaskan Native	1 (<1)	6 (<1)	11 (<1)	0	0	17 (<1)	6 (<1)
Native Hawaiian or Other Pacific Islander	3 (2)	11 (1)	21 (2)	6 (1)	4 (3)	42 (2)	25 (2)
Other	10 (7)	11 (1)	53 (4)	37 (7)	9 (7)	110 (4)	51 (4)
Missing	0	0	0	0	0	0	2 (<1)
Age (years)							
N	134	757	1279	520	134	2690	1277
<45	36 (27)	192 (25)	353 (28)	150 (29)	33 (25)	728 (27)	346 (27)
45 to <65	79 (59)	450 (59)	718 (56)	287 (55)	71 (53)	1526 (57)	717 (56)
65 to <75	12 (9)	89 (12)	165 (13)	67 (13)	19 (14)	340 (13)	168 (13)
≥75	7 (5)	26 (3)	43 (3)	16 (3)	11 (8)	96 (4)	46 (4)
Mean±SD	51.5±12.18	52.5±11.68	52.3±11.90	51.6±11.83	54.3±12.83	52.3±11.88	52.4±12.03
Range	26-82	21-85	21-85	23-81	30-82	21-85	19-85
BMI (kg/m^2)							
N	134	755	1278	519	134	2686	1272
<18.5	0	0	1 (<1)	0	0	1 (<1)	1 (<1)
18.5 to <25	16 (12)	50 (7)	71 (6)	23 (4)	9 (7)	153 (6)	64 (5)
25 to <30	48 (36)	215 (28)	392 (31)	168 (32)	42 (31)	817 (30)	416 (33)
≥30	70 (52)	490 (65)	814 (64)	328 (63)	83 (62)	1715(64)	791 (62)
Missing	0	2 (<1)	1 (<1)	1 (<1)	0	4 (<1)	5 (<1)
Mean±SD	31.8±6.32	32.9±6.37	32.8±6.21	32.8±6.16	32.8±6.55	32.9±6.26	32.6±6.12
Range	21.8-53.2	19.9-64.4	16.0-64.3	20.7-63.5	21.0-64.6	16.0-64.6	16.8-64.1
Alcohol Drinker	87 (65)	515 (68)	864 (68)	330 (63)	79 (59)	1788 (66)	885 (69)
Tobacco User	32 (24)	132 (17)	246 (19)	99 (19)	24 (18)	501 (19)	224 (18)
Low-Dose Aspirin Use[b]	31 (23)	133 (18)	218 (17)	91 (18)	34 (25)	476 (18)	208 (16)
Renal Function (mL/min)[a]							
Normal	67 (50)	278 (37)	512 (40)	257 (49)	70 (52)	1117 (42)	514 (40)
Mild Impairment	50 (37)	349 (46)	573 (45)	185 (36)	38 (28)	1145 (43)	558 (44)
Moderate Impairment	17 (13)	130 (17)	194 (15)	78 (15)	26 (19)	428 (16)	205 (16)
Nephrolithiasis	3 (2)	44 (6)	76 (6)	26 (5)	3 (2)	149 (6)	67 (5)
At least 1 Cardiovascular Risk Factor [c]	115 (86)	673 (89)	1145 (90)	457 (88)	118 (88)	2393 (89)	1150 (90)

Studies included are APEX, FACT and CONFIRMS. SD = standard deviation.

a Normal renal function (CrCl ≥90 mL/min); mild renal impairment (CrCl 60-89 mL/min); moderate renal impairment (CrCl 30-59 mL/min). Fourteen subjects had CrCl <30 mL/min; those subjects were included in the moderate renal impairment group.

b Defined as a total dose <325 mg/day that was ongoing at the time of study completion.

c See Table 42 in the Cardiovascular Adverse Event Section for a list of the CV risk factors and percentages for each type of risk.

8.3.3 Adverse Events - Phase 3 Controlled Studies

In this section, AEs will be discussed by Medical Dictionary for Regulatory Activities (MedDRA) High Level Terms. As considered clinically relevant to the assessment, the related

Preferred Terms that contribute to the rate of events in a High Level Term grouping are provided in a footnote and/or in-text.

Table 35 shows the percentage of subjects who experienced at least one AE during the individual Phase 3 controlled studies. The incidence of AEs was similar across treatment groups within a study. Comparing across studies, the incidence of AEs was higher in the 52-week FACT Study compared to the 28-week APEX and 6-month CONFIRMS Studies, as would be expected with a longer study period.

Table 35 Summary of Subjects With At Least 1 Adverse Event (Phase 3 Controlled Studies)

Study	Placebo % (n/N)	Febuxostat 40 mg % (n/N)	Febuxostat 80 mg % (n/N)	Febuxostat 120 mg % (n/N)	Febuxostat 240 mg % (n/N)	Allopurinol % (n/N)
APEX	72 (97/134)	NE	68 (181/267)	68 (183/269)	73 (98/134)	75 (200/268)
FACT	NE	NE	80 (205/256)	75 (189/251)	NE	85 (215/253)
CONFIRMS	NE	57 (429/757)	54 (410/756)	NE	NE	57 (433/756)
TOTAL	**72 (97/134)**	**57 (429/757)**	**62 (797/1279)**	**72 (372/520)**	**73 (98/134)**	**66 (848/1277)**

NE = treatment/dose not evaluated.

The most frequently reported AEs (≥5% of subjects) are summarized in Table 36. Combining data across the Phase 3 controlled studies for each of the treatment groups, no dose-related trends were observed. The incidence of diarrhea in each treatment group was similar to placebo, except for febuxostat 240 mg, which may have been related to a known side-effect of colchicine.[70] The liver function analyses were higher in the active treatment (febuxostat and allopurinol) groups compared to placebo.

Table 36 Most Frequently Reported (≥5% of Subjects) Treatment-Emergent Adverse Events by High Level Term (Phase 3 Controlled Studies)

MedDRA High Level Term	Placebo N=134 n (%)	Febuxostat 40 mg N=757 n (%)	Febuxostat 80 mg N=1279 n (%)	Febuxostat 120 mg N=520 n (%)	Febuxostat 240 mg N=134 n (%)	Allopurinol N=1277 n (%)
Subjects who had at least 1 AE	**97 (72)**	**429 (57)**	**797 (62)**	**372 (72)**	**98 (73)**	**848 (66)**
Upper respiratory tract infections	21 (16)	71 (9)	169 (13)	103 (20)	27 (20)	182 (14)
Musculoskeletal and connective tissue signs and symptoms	14 (10)	43 (6)	99 (8)	72 (14)	14 (10)	99 (8)
Diarrhea (excl infective)	12 (9)	45 (6)	94 (7)	45 (9)	20 (15)	91 (7)
Liver function analyses[a]	3 (2)	63 (8)	82 (6)	26 (5)	6 (4)	77 (6)
Joint related signs and symptoms	6 (4)	31 (4)	81 (6)	43 (8)	7 (5)	77 (6)
Headaches NEC[b]	7 (5)	21 (3)	53 (4)	38 (7)	12 (9)	62 (5)
Nausea and vomiting symptoms	5 (4)	22 (3)	47 (4)	23 (4)	8 (6)	28 (2)
Vascular hypertensive disorders	8 (6)	15 (2)	37 (3)	17 (3)	7 (5)	37 (3)
Non-site specific injuries	2 (1)	6 (<1)	35 (3)	14 (3)	7 (5)	23 (2)
Neurological signs and symptoms[c]	2 (1)	18 (2)	34 (3)	13 (3)	7 (5)	20 (2)
Gastrointestinal and abdominal pains (excl oral and throat)	3 (2)	11 (1)	29 (2)	13 (3)	8 (6)	26 (2)
Influenza viral infections	6 (4)	7 (<1)	27 (2)	27 (5)	7 (5)	26 (2)
Muscle related signs and symptoms	7 (5)	4 (<1)	10 (<1)	7 (1)	2 (1)	20 (2)

Studies included are APEX, FACT, and CONFIRMS.
MedDRA = Medical Dictionary for Regulatory Activities; NEC = not elsewhere classified in MedDRA.
a This included all reactions reported by investigator as AEs, regardless of magnitude of elevation.
b MedDRA preferred terms reported for headaches: cluster headache, headache, sinus headache, and tension headache.
c MedDRA preferred terms reported for neurological signs and symptoms: dizziness, dizziness postural, dysgeusia, and presyncope.

8.3.4 Deaths - Phase 3 Controlled Studies

One subject died during the Screening period for the CONFIRMS Study; this subject died due to a myocardial infarction. Nine subjects died after randomization in two of the Phase 3 controlled studies. Of the nine subjects who died after randomization, five subjects died during the 6-month CONFIRMS Study (one subject on febuxostat 40 mg, one subject on febuxostat 80 mg, and three subjects on allopurinol); and four subjects died during the 52-week FACT Study (two subjects on febuxostat 80 mg, two on febuxostat 120 mg, and none on allopurinol). There were no deaths in the 28-week APEX Study. No patterns were seen for the timing of onset or cause of death.

The rate of death was the same in the total febuxostat and allopurinol groups at 0.2% of subjects in both groups. The cause of death is provided in Table 37.

Table 37 Deaths (Phase 3 Controlled Studies)

Deaths	Placebo N=134 PY=59.9	Febuxostat 40 mg N=757 PY=343.1	Febuxostat 80 mg N=1279 PY=644.4	Febuxostat 120 mg N=520 PY=304.5	Febuxostat 240 mg N=134 PY=54.0	Febuxostat Total N=2690 PY=1346.0	Allopurinol N=1277 PY=670.9
Number of deaths	0	1	3	2	0	6	3
Rate (%) [95% CI][a]	[0.000-2.715]	0.13% [0.003-0.734]	0.23% [0.048-0.684]	0.38% [0.047-1.382]	[0.000-2.715]	0.22% [0.082-0.485]	0.23% [0.048-0.685]
APEX Study (No Deaths)							
FACT Study							
Retroperitoneal hemorrhage			1			1	
Respiratory failure			1			1	
Resp failure/anoxic encephalopathy				1		1	
Colon cancer				1		1	
CONFIRMS Study							
Anaphylactic reaction		1[b]				1	
Brain edema/COPD			1			1	
Hypertensive Heart disease							1
Sudden death							1
Lung adenocarcinoma/ pneumonia/sepsis							1

COPD = chronic obstructive pulmonary disease; resp = respiratory.
a 95% CIs for the incidence rate are calculated based on binomial distribution.
b The anaphylactic reaction was due to multiple ant bites.

8.3.5 Other Serious Adverse Events - Phase 3 Controlled Studies

The incidence of SAEs in the febuxostat 80 mg group was consistent across the three studies despite differences in treatment duration (Table 38). However, the incidence of SAEs for febuxostat 120 mg and allopurinol were higher in the FACT Study compared to the APEX Study. Combining data from the Phase 3 controlled studies, the incidence of SAEs in the active treatment groups was lowest in the febuxostat 40 mg group (2.5%) and the febuxostat 80 mg (3.8%) was similar to allopurinol (4.4%).

Table 38 Summary of Subjects With At Least 1 Serious Adverse Event (Phase 3 Controlled Studies)

Study	Placebo % (n/N)	Febuxostat 40 mg % (n/N)	Febuxostat 80 mg % (n/N)	Febuxostat 120 mg % (n/N)	Febuxostat 240 mg % (n/N)	Allopurinol % (n/N)
APEX	1.5 (2/134)	NE	4.1 (11/267)	3.3 (9/269)	3.7 (5/134)	2.6 (7/268)
FACT	NE	NE	3.9 (10/256)	7.6 (19/251)	NE	7.1 (18/253)
CONFIRMS	NE	2.5 (19/757)	3.7 (28/756)	NE	NE	4.1 (31/756)
TOTAL	**1.5 (2/134)**	**2.5 (19/757)**	**3.8 (49/1279)**	**5.4 (28/520)**	**3.7 (5/134)**	**4.4 (56/1277)**

NE= treatment/dose not evaluated.

Coronary artery disorders (ischemic and coronary artery disorders not otherwise classified) were the most common types of SAEs (Table 39). The incidence was comparable in the placebo, febuxostat 80 mg, febuxostat 120 mg and allopurinol groups (0.7-0.8%), and lowest in the febuxostat 40 mg (0.4%) and 240 mg groups (0%). See Section 8.3.8.1 for an in-depth discussion of cardiovascular events.

Table 39 Serious Adverse Events (≥0.3% of Subjects in Any Group) (Phase 3 Controlled Studies)

MedDRA High Level Term	Placebo N=134 n (%)	Febuxostat 40 mg N=757 n (%)	Febuxostat 80 mg N=1279 n (%)	Febuxostat 120 mg N=520 n (%)	Febuxostat 240 mg N=134 n (%)	Allopurinol N=1277 n (%)
Ischemic coronary artery disorders[a]	0	1 (0.1)[c]	6 (0.5)	4 (0.8)	0	3 (0.2)
Coronary artery disorders NEC[b]	1 (0.7)	2 (0.3)	2 (0.2)	0	0	6 (0.5)
Pain and discomfort	0	1 (0.1)	4 (0.3)	1 (0.2)	0	2 (0.2)
Heart failure NEC	0	2 (0.3)	3 (0.2)	1 (0.2)	0	1 (<0.1)
Intestinal ulcers and perforation	0	2 (0.3)	1 (<0.1)	1 (0.2)	0	1 (<0.1)
Abdominal and gastrointestinal infections	0	2 (0.3)	0	1 (0.2)	0	4 (0.3)
Cholecystitis and cholelithiasis	0	0	0	0	0	4 (0.3)
Disturbances in consciousness	0	0	0	1 (0.2)	0	4 (0.3)

Studies included APEX, FACT, and CONFIRMS.
MedDRA = Medical Dictionary for Regulatory Activities; NEC = not elsewhere classified in MedDRA.
a MedDRA Preferred terms were acute coronary syndrome, acute myocardial infarction, angina pectoris, unstable angina, myocardial infarction.
b MedDRA Preferred terms: arteriosclerosis coronary artery, coronary artery disease, coronary artery occlusion, coronary artery arthrosclerosis.
c This subject was also counted in the coronary artery disorders "not elsewhere classified" (NEC).

8.3.6 Discontinuation Due to Adverse Events - Phase 3 Controlled Studies

The proportion of subjects who discontinued in association with one or more AEs are shown by study and treatment in Table 40. Despite differences in treatment duration, the incidence of

discontinuation due to an AE was very consistent across studies for the febuxostat 80 mg group, which was included in all three studies. Combining data from the three studies, the incidence of discontinuations due to AEs appeared to increase with increasing dose of febuxostat. The proportions of subjects discontinuing due to AEs while on febuxostat 40 mg and 80 mg, the recommended doses, were comparable to subjects on allopurinol.

Table 40 Summary of Subjects Who Discontinued Due to an Adverse Event (Phase 3 Controlled Studies)

Study	Placebo % (n/N)	Febuxostat 40 mg % (n/N)	Febuxostat 80 mg % (n/N)	Febuxostat 120 mg % (n/N)	Febuxostat 240 mg % (n/N)	Allopurinol % (n/N)
APEX	5.2 (7/134)	NE	7.5 (20/267)	7.1 (19/269)	9.7 (13/134)	6.7 (18/268)
FACT	NE	NE	7.4 (19/256)	10.0 (25/251)	NE	3.2 (8/253)
CONFIRMS	NE	6.2 (47/757)	7.8 (59/756)	NE	NE	8.1 (61/756)
TOTAL	**5.2 (7/134)**	**6.2 (47/757)**	**7.7 (98/1279)**	**8.5 (44/520)**	**9.7 (13/134)**	**6.8 (87/1277)**

NE = treatment/dose not evaluated.

The most common type of AE that led to discontinuation was liver function analyses (1.8%, 1.4%, 1.9%, 0%, and 0.9%, in the febuxostat 40 mg, 80 mg, 120 mg, 240 mg and allopurinol groups, respectively), followed by diarrhea (0.8%, 0.8%, 0.2%, 3.0%, and 0.7%, respectively). Subjects could be discontinued at the discretion of the investigator regardless of the magnitude of the liver function values. Subjects with treatment-emergent elevations in liver function tests are discussed in the Clinical Laboratory Evaluations (Section 8.5.1). Three of the four subjects in the 240 mg febuxostat group who discontinued due to diarrhea were on colchicine for gout flare prophylaxis; colchicine is known to cause diarrhea.[70]

8.3.7 Subgroup Analysis by Renal Function

Renal impairment is common in subjects with gout[64,68] and 59% of subjects in the febuxostat Phase 3 controlled studies had mild or moderate renal impairment at baseline. Therefore, in this section, AEs, SAEs, and discontinuations due to AEs are summarized by baseline renal function subgroups to assess whether there are differences in tolerance to febuxostat between subjects with renal impairment and subjects with normal renal function. The incidence of renal AEs and changes in renal laboratory values for the safety population as a whole are discussed in Section 8.3.8.3.

The renal function subgroups were defined: normal renal function = CrCl ≥90 mL/min; mild renal impairment = CrCl 60-89 mL/min; and moderate renal impairment = CrCl 30-59 mL/min, where CrCl was calculated using the Cockcroft-Gault formula corrected for Ideal Body Weight (IBW) at Screening.[65] Patients with severe renal impairment (CrCl <30 mL/min) were excluded from study participation.

The CONFIRMS Study was the only controlled study that enrolled subjects with renal impairment based on prospectively defined criteria and had prespecified analysis by baseline renal function. Therefore, the CONFIRMS Study allows a robust analysis and is the primary source of data for the safety evaluation of febuxostat by baseline renal function discussed in this section. However, these data were also evaluated for the combined Phase 3 controlled studies.

8.3.7.1 Demographic and Baseline Characteristics by Renal Function

Subjects with moderate renal impairment tended to be older, to weigh less, and have a higher incidence of CV risk factors than subjects with normal renal function.

8.3.7.2 Adverse Events by Renal Function

Upper respiratory tract infections, liver function analyses, and diarrhea were the most common types of AEs regardless of renal function status. The types of AEs reported by subjects with moderate renal impairment were similar to those for subjects with normal or mild impairment renal function, as shown in Table 41.

Table 41 Most Frequent AEs (≥5% in at least one treatment group) by Renal Status (CONFIRMS Study)

	Febuxostat									Allopurinol		
	40 mg			80 mg			Total					
MedDRA High Level Term	Norm. N=278 n (%)	Mild N=349 n (%)	Mod. N=130 n (%)	Norm. N=253 n (%)	Mild N=367 n (%)	Mod. N=136 n (%)	Norm. N=531 n (%)	Mild N=716 n (%)	Mod. N=266 n (%)	Norm. N=255 n (%)	Mild N=365 n (%)	Mod. N=136 n (%)
Total subjects with ≥1 AE	**161 (58)**	**191 (55)**	**77 (59)**	**140 (55)**	**194 (53)**	**76 (56)**	**301 (57)**	**385 (54)**	**153 (58)**	**144 (56)**	**203 (56)**	**86 (63)**
Upper Respiratory Tract Infections	30 (11)	34 (10)	7 (5)	15 (6)	28 (8)	10 (7)	45 (8)	62 (9)	17 (6)	17 (7)	30 (8)	10 (7)
Liver Function Analyses	29 (10)	26 (7)	8 (6)	24 (9)	21 (6)	7 (5)	53 (10)	47 (7)	15 (6)	22 (9)	24 (7)	4 (3)
Diarrhea (Excl Infective)	15 (5)	19 (5)	11 (8)	16 (6)	17 (5)	14 (10)	31 (6)	36 (5)	25 (9)	21 (8)	27 (7)	9 (7)
Musculoskeletal and Connective Tissue Signs and Symptoms	10 (4)	21 (6)	12 (9)	12 (5)	19 (5)	7 (5)	22 (4)	40 (6)	19 (7)	10 (4)	15 (4)	7 (5)
Joint Related Signs and Symptoms NEC	10 (4)	17 (5)	4 (3)	5 (2)	18 (5)	10 (7)	15 (3)	35 (5)	14 (5)	8 (3)	11 (3)	4 (3)
Neurological Signs and Symptoms	4 (1)	7 (2)	7 (5)	1 (<1)	7 (2)	5 (4)	5 (<1)	14 (2)	12 (5)	2 (<1)	5 (1)	0
Edema NEC	4 (1)	4 (1)	2 (2)	2 (<1)	4 (1)	5 (4)	6 (1)	8 (1)	7 (3)	1 (<1)	10 (3)	7 (5)
Lower Respiratory Tract and Lung Infections	4 (1)	3 (<1)	2 (2)	3 (1)	9 (2)	2 (1)	7 (1)	12 (2)	4 (2)	2 (<1)	8 (2)	7 (5)
Rashes, Eruptions and Exanthemas NEC	3 (1)	3 (<1)	7 (5)	7 (3)	7 (2)	1 (<1)	10 (2)	10 (1)	8 (3)	5 (2)	2 (<1)	3 (2)

MedDRA = Medical Dictionary for Regulatory Activities; NEC = not elsewhere classified in MedDRA; Norm = normal; Mod = moderate.

Note: Normal (Norm.) renal function: CrCl = ≥90 mL/min; mild renal impairment: CrCl = 60-89 mL/min; and moderate (Mod.) renal impairment: CrCl = 30-59 mL/min. The moderate renal impairment group includes the 2 subjects who had CrCl <30 mL/min.

8.3.7.3 Serious Adverse Events by Renal Function

Serious adverse events occurred at a higher rate in the CONFIRMS Study in subjects with moderate renal impairment than in subjects with mild renal impairment or normal renal function. This pattern was similar across all treatment groups, including allopurinol. The incidence of SAEs was 6%, 6%, and 12% of subjects with moderate renal impairment for the febuxostat 40 mg, febuxostat 80 mg, and allopurinol groups, respectively, while the incidences of SAEs in subjects with normal function were 2%, 3%, and 3% and with mild renal impairment were 2%, 4%, and 2%, respectively. No difference in the pattern or the type of SAEs was identified across treatment groups for all renal function subgroups.

8.3.7.4 Discontinuations Due to AEs by Renal Function

Discontinuations due to AEs in the CONFIRMS Study were higher in subjects with moderate renal impairment (11%, 13%, and 13%) than those with mild impairment (6%, 7%, and 6%) and those with normal renal function (5%, 7%, and 9%) in the febuxostat 40 mg, 80 mg and allopurinol groups in the CONFIRMS Study. The most common AEs that led to discontinuation of subjects with moderate renal impairment were diarrhea (2%, 2%, and 0%), rash (2%, 0%, 1%) and liver function analyses (1%, 1%, and 0% for febuxostat 40 mg, 80 mg, and allopurinol, respectively). Diarrhea and liver function analyses were also the most common reasons for discontinuation of subjects with normal function or mild renal impairment.

8.3.7.5 Conclusions from Renal Function Subgroup Analysis

Febuxostat was well-tolerated in subjects with moderate or mild renal impairment compared to subjects with normal renal function; potential subjects with severe renal impairment were excluded from the studies. There was a small increase in AEs in subjects with moderate renal impairment compared to subjects with normal renal function in all the treatment groups, including allopurinol. Therefore, this increase did not appear related to study drug. Note also that the same pattern was observed in the combined Phase 3 controlled studies as in the CONFIRMS Study.

8.3.8 Adverse Events by Organ System or Syndrome

Adverse events affecting certain organ systems were selected for in-depth review because of the known high prevalence of certain comorbidities in the gout population (CV disease and renal insufficiency) or because of known side effects (hepatotoxicity and cutaneous rash) of the XO inhibitor, allopurinol.[68]

8.3.8.1 Cardiovascular Adverse Events

Almost all subjects (89%) in the Phase 3 controlled studies had at least one CV risk factor and 30% of the subjects had at least 3 CV risk factors, a combination of comorbidities and life-style factors (Table 42). A majority of subjects (64%) had at least one CV medical condition. The incidence of CV risk factors was similar across treatment groups.

Table 42 Baseline Cardiovascular Risk Factors by Number of Factors (Phase 3 Controlled Studies)

	Placebo (N=134) n (%)	Febuxostat					Allopurinol (N=1277) n (%)
		40 mg (N=757) n (%)	80 mg (N=1279) n (%)	120 mg (N=520) n (%)	240 mg (N=134) n (%)	Total (N=2690) n (%)	
Subjects With ≥1 Cardiovascular Risk Factor[a]	**115 (86)**	**673 (89)**	**1145 (90)**	**457 (88)**	**118 (88)**	**2393 (89)**	**1150 (90)**
At least 1 of the following Medical Conditions	80 (60)	495 (65)	816 (64)	314 (60)	87 (65)	1712 (64)	845 (66)
Atherosclerotic Disease	18 (13)	83 (11)	148 (12)	65 (13)	24 (18)	320 (12)	143 (11)
Congestive Heart Failure	5 (4)	21 (3)	28 (2)	10 (2)	6 (4)	65 (2)	20 (2)
Diabetes	9 (7)	89 (12)	149 (12)	46 (9)	12 (9)	296 (11)	150 (12)
Hypertension	61 (46)	388 (51)	634 (50)	239 (46)	71 (53)	1332 (50)	647 (51)
Hyperlipidemia	44 (33)	299 (39)	490 (38)	169 (33)	49 (37)	1007 (37)	501 (39)
Myocardial Infarction	7 (5)	23 (3)	56 (4)	33 (6)	9 (7)	121 (4)	38(3)
Stroke	3 (2)	3 (<1)	7 (<1)	6 (1)	4 (3)	20 (<1)	13 (1)
Transient Ischemic Attack	2 (1)	7 (<1)	12 (<1)	3 (<1)	3 (2)	25 (<1)	17 (1)
≥1 of the following Lifestyle Risk Factors	83 (62)	534 (71)	902 (71)	366 (70)	91 (68)	1893 (70)	883 (69)
BMI ≥30 kg/m^2	70 (52)	490 (65)	814 (64)	328 (63)	83 (62)	1715 (64)	791 (62)
Tobacco User	32 (24)	132 (17)	246 (19)	99 (19)	24 (18)	501 (19)	224 (18)
Subjects By Number of Cardiovascular Risk Factors[a]							
1-2 Risk Factors	75 (56)	440 (58)	747 (58)	304 (58)	69 (51)	1560 (58)	776 (61)
3-4 Risk Factors	34 (25)	195 (26)	330 (26)	133 (26)	37 (28)	695 (26)	305 (24)
≥5 Risk Factors	6 (4)	38 (5)	68 (5)	20 (4)	12 (9)	138 (5)	69 (5)

Studies included are APEX, FACT, and CONFIRMS.

a Included medical history and/or lifestyle risk factors.

As noted previously, increased sUA levels are associated with an increased risk of cardiovascular disease.[26,34,71-73]

In the APEX and FACT studies, as well as the open-label, long-term extension studies, there was a numerical imbalance in the febuxostat and allopurinol groups in the small number of cardiovascular/thromboembolic events reported. An adjudication process was developed to thoroughly assess and characterize CV AEs. Adverse events were identified by reviewing the safety database for unique MedDRA Preferred Terms that had a relationship to the CV system, regardless of underlying pathology. A consulting CV expert (Dr. William B. White, Professor, Calhoun Cardiology Center, University of Connecticut School of Medicine, Farmington, CT) performed a blinded adjudication of retrospectively identified AEs that were potentially CV in nature, using criteria proposed by the APTC[19] and modified by White et al.[20]

For the CONFIRMS Study, the CV adjudication was performed prospectively by an independent Cardiovascular Endpoints Committee that consisted of three members (two cardiologists and one neurologist) after a formal Charter had been developed. Cardiovascular worksheets were provided to the investigational sites to ensure consistent and standardized collection of relevant information necessary for a thorough assessment and adjudication of all potential CV events and all deaths. The completed worksheets, along with supporting documentation for each event, were sent to the three members simultaneously. Each committee member completed individual reviews and adjudications, and when assessments differed, the case was reviewed by the committee to establish a consensus diagnosis.

The output of the adjudication process was to assign APTC events into the following categories:

- Cardiovascular Death
- Nonfatal Myocardial Infarction
- Nonfatal Stroke

Non-APTC CV events were adjudicated similarly and assigned as follows:

- Angina

- Coronary Revascularization
- Transient Ischemic Attack
- Cerebral Revascularization
- Venous and Peripheral Arterial Vascular Thrombotic Events
- Nonfatal Congestive Heart Failure
- Arrhythmia without Evidence of Ischemia
- Other Non-APTC CV Events (eg, severe hypertension, syncope)

In the CONFIRMS Study, potential CV events were prospectively adjudicated including events that occurred during the Screening Period prior to randomization. Seven subjects experienced nine SAEs in the Screening Period that were identified as potentially CV in nature. One subject experienced an event of fatal myocardial infarction adjudicated as a CV death. Three subjects were adjudicated to non-APTC CV diagnoses, including nonfatal congestive heart failure, arrhythmia (atrial fibrillation), and peripheral thrombotic events (bowel ischemia, occlusion of mesenteric arteries, and stenosis of celiac trunk). The remaining three subjects experienced events of bradycardia, sudden collapse, and uncontrolled hypertension.

In this section the APTC and non-APTC CV events that occurred in randomized subjects in the CONFIRMS Study will be discussed first, followed by a discussion of events that occurred in all three Phase 3 controlled studies.

8.3.8.1.1 Adjudicated APTC and Non-APTC CV Events - CONFIRMS Study

8.3.8.1.1.1 Adjudicated APTC Events - CONFIRMS Study

In the CONFIRMS Study, 3 subjects (0.4%) in the febuxostat 80 mg group and 3 subjects (0.4%) in the allopurinol groups experienced an adjudicated APTC event, compared to no subject in the febuxostat 40 mg group (Table 43).

Table 43 Subjects With Adjudicated APTC Events (CONFIRMS Study)

APTC Criterion	Febuxostat 40 mg (N=757)	Febuxostat 80 mg (N=756)	Febuxostat Total (N=1513)	Allopurinol (N=756)
All APTC Events				
Number of Subjects	0	3	3	3
Rate (%)	0	0.40	0.20	0.40
95% CI[a]	0.000-0.486	0.082-1.155	0.041-0.578	0.082-1.155
Cardiovascular Death				
Number of Subjects	0	0	0	2
Rate (%)	0	0	0	0.26
95% CI[a]	0.000-0.486	0.000-0.487	0.000-0.244	0.032-0.952
Nonfatal Myocardial Infarction				
Number of Subjects	0	1	1	1
Rate (%)	0	0.13	0.07	0.13
95% CI[a]	0.000-0.486	0.003-0.735	0.002-0.368	0.003-0.735
Nonfatal Stroke				
Number of Subjects	0	2	2	0
Rate (%)	0	0.26	0.13	0
95% CI[a]	0.000-0.486	0.032-0.952	0.016-0.477	0.000-0.487

a The confidence intervals are calculated based on binomial distribution.

None of the APTC events in the febuxostat 80 mg group resulted in death. Two APTC events in the allopurinol group resulted in deaths. A third allopurinol subject, who had a nonfatal myocardial infarction, was discontinued due to noncompliance with study drug.

Two subjects in the febuxostat 80 mg group experienced events adjudicated as nonfatal stroke. One subject discontinued due to the event, and the other subject continued treatment and completed the study. A third subject in the febuxostat 80 mg group experienced a nonfatal myocardial infarction; the subject continued treatment and completed the study.

8.3.8.1.1.2 Adjudicated Non-APTC CV Events - CONFIRMS Study

Adjudicated non-APTC CV events were reported for 10 (1.3%) subjects in the febuxostat 40 mg, 9 (1.2%) in the febuxostat 80 mg, and 7 (0.9%) subjects in the allopurinol groups. All of these subjects had underlying CV risk factors. A summary of the types of non-APTC CV events is provided by treatment group in Table 44.

Of the 26 subjects who had non-APTC CV events, 14 subjects had events that were considered SAEs: 5 on febuxostat 40 mg; 5 on febuxostat 80 mg, and 4 on allopurinol. Seven of these

14 subjects with serious non-APTC CV events discontinued study drug due to the event (2 on febuxostat 40 mg; 3 on febuxostat 80 mg; and 2 on allopurinol).

Table 44 Analyses of Subjects With Adjudicated Non-APTC CV Events (CONFIRMS Study)

Non-APTC CV Criterion	Febuxostat 40 mg (N=757)	Febuxostat 80 mg (N=756)	Febuxostat Total (N=1513)	Allopurinol (N=756)
All Non-APTC CV Events				
Number of Subjects	10	9	19	7
Rate (%)	1.32	1.19	1.26	0.93
95% CI[a]	0.635-2.416	0.546-2.248	0.758-1.954	0.373-1.898
Arrhythmia, No Evidence of Ischemia				
Number of Subjects	3	4	7	1
Rate (%)	0.40	0.53	0.46	0.13
95% CI[a]	0.082-1.154	0.144-1.349	0.186-0.951	0.003-0.735
Venous and Peripheral Arterial Vascular Thrombotic Events				
Number of Subjects	0	2	2	0
Rate (%)	0.00	0.26	0.13	0.00
95% CI[a]	0.000-0.486	0.032-0.952	0.016-0.477	0.000-0.487
Nonfatal Congestive Heart Failure				
Number of Subjects	2	0	2	1
Rate (%)	0.26	0.00	0.13	0.13
95% CI[a]	0.032-0.951	0.000-0.487	0.016-0.477	0.003-0.735
Angina				
Number of Subjects	2	0	2	0
Rate (%)	0.26	0.00	0.13	0.00
95% CI[a]	0.032-0.951	0.000-0.487	0.016-0.477	0.000-0.487
Coronary Revascularization				
Number of Subjects	1	0	1	1
Rate (%)	0.13	0.00	0.07	0.13
95% CI[a]	0.003-0.734	0.000-0.487	0.002-0.368	0.003-0.735
Transient Ischemic Attack				
Number of Subjects	1	0	1	1
Rate (%)	0.13	0.00	0.07	0.13
95% CI[a]	0.003-0.734	0.000-0.487	0.002-0.368	0.003-0.735
Cerebral Revascularization				
Number of Subjects	0	0	0	0
Rate (%)	0.00	0.00	0.00	0.00
95% CI[a]	0.000-0.486	0.000-0.487	0.000-0.244	0.000-0.487
Other Non-APTC CV Events[b]				
Number of Subjects	1	3	4	3
Rate (%)	0.13	0.40	0.26	0.40
95% CI[a]	0.003-0.734	0.082-1.155	0.072-0.676	0.082-1.155

a The confidence intervals are calculated based on binomial distribution.

b Three subjects experienced hypertension (1 in febuxostat 40 mg, 2 in febuxostat 80 mg, and 1 in allopurinol groups), 1 subject (in the febuxostat 80 mg group) experienced hypotension, 1 subject (in the allopurinol group) experienced a new left bundle branch block, and 1 subject (in the allopurinol group) experienced syncope of a cardiovascular nature.

The most common type of non-APTC CV event was arrhythmia with no evidence of ischemia. The majority of these were atrial arrhythmias. Three subjects on febuxostat 80 mg experienced SAEs of arrhythmia. Two of the three discontinued due to the events (one with atrioventricular (A-V) block, and one with atrial fibrillation). The other subject who experienced an SAE of A-V block completed the study. The remaining atrial arrhythmias were nonserious with three subjects experiencing atrial fibrillation (1 event each on febuxostat 40 mg, febuxostat 80 mg, and allopurinol). The subject on 80 mg discontinued due to the event, while the other two completed the study.

The remaining two subjects with arrhythmia experienced either nonserious, transient atrial flutter or ventricular extrasystoles; both were on febuxostat 40 mg and completed the study.

8.3.8.1.2 Adjudicated APTC and Non-APTC CV Events - Phase 3 Controlled Studies

8.3.8.1.2.1 Adjudicated APTC Events - Phase 3 Controlled Studies

The incidence of adjudicated APTC events in each of the Phase 3 controlled studies are shown in Table 45.

Febuxostat doses differed across the Phase 3 controlled studies, with febuxostat 80 mg evaluated in all three studies. Compared to allopurinol, there was a higher incidence of APTC events in the 80 mg group in the APEX and FACT Studies that was not observed in the CONFIRMS Study. The incidence of APTC events in the 80 mg group was the same in the APEX and CONFIRMS Studies, but higher in the FACT Study. Reviewing the time to onset of events, there was no clustering of events in these studies. In the FACT study, the events were evenly distributed throughout the 52-week treatment period with 3 events occurring in the first 6 months and the other 3 in the last 6 months.

Table 45 Adjudicated APTC Events (Phase 3 Controlled Studies)

Study	Placebo % (n/N)	Febuxostat 40 mg % (n/N)	Febuxostat 80 mg % (n/N)	Febuxostat 120 mg % (n/N)	Febuxostat 240 mg % (n/N)	Allopurinol % (n/N)
APEX	0.0 (0/134)	NE	0.4 (1/267)	0.4 (1/269)	0.0 (0/134)	0.0 (0/268)
FACT	NE	NE	1.2 (3/256)	0.8 (2/251)	NE	0.4 (1/253)
CONFIRMS	NE	0.0 (0/757)	0.4 (3/756)	NE	NE	0.4 (3/756)
Total	**0.0 (0/134)**	**0.0 (0/757)**	**0.55 (7/1279)**	**0.58 (3/520)**	**0.0 (0/134)**	**0.31 (4/1277)**
95% CI	**0.00-2.72**	**0.00-0.49**	**0.22-1.12**	**0.12-1.68**	**0.00-2.72**	**0.09-0.80**

NE = treatment/dose not evaluated.

The rates of individual types of APTC events are shown in Table 46. There are too few events to draw any meaningful comparisons across treatments. Five subjects experienced events adjudicated to be CV deaths, which were discussed in Section 8.3.4. The 2 subjects who had a nonfatal stroke were enrolled in the CONFIRMS Study and discussed in Section 8.3.8.1.1.1.

Table 46 Analyses of Subjects With Adjudicated APTC Events (Phase 3 Controlled Studies)

APTC Criterion	Placebo (N=134)	Febuxostat					Allopurinol (N=1277)
		40 mg (N=757)	80 mg (N=1279)	120 mg (N=520)	240 mg (N=134)	Total (N=2690)	
All APTC Events							
Number of Subjects	0	0	7	3	0	10	4
Rate (%)	0.00	0.00	0.55	0.58	0.00	0.37	0.31
95% CI[a]	0.000-2.715	0.000-0.486	0.220-1.124	0.119-1.677	0.000-2.715	0.178-0.683	0.085-0.800
Cardiovascular Death							
Number of Subjects	0	0	2	1	0	3	2
Rate (%)	0.00	0.00	0.16	0.19	0.00	0.11	0.16
95% CI[a]	0.000-2.715	0.000-0.486	0.019-0.564	0.005-1.067	0.000-2.715	0.023-0.326	0.019-0.565
Nonfatal Myocardial Infarction							
Number of Subjects	0	0	3	2	0	5	2
Rate (%)	0.00	0.00	0.23	0.38	0.00	0.19	0.16
95% CI[a]	0.000-2.715	0.000-0.486	0.048-0.684	0.047-1.382	0.000-2.715	0.060-0.433	0.019-0.565
Nonfatal Stroke							
Number of Subjects	0	0	2	0	0	2	0
Rate (%)	0.00	0.00	0.16	0.00	0.00	0.07	0.00
95% CI[a]	0.000-2.715	0.000-0.486	0.019-0.564	0.000-0.707	0.000-2.715	0.009-0.268	0.000-0.288

Studies included are APEX, FACT, and CONFIRMS.

a The confidence intervals are calculated based on binomial distribution.

Five of the seven subjects who experienced a nonfatal myocardial infarction continued on study drug and completed the study (4 on febuxostat and 1 on allopurinol). One subject in the febuxostat 120 mg group discontinued study drug due to the myocardial infarction. The other subject, who was in the allopurinol group, was discontinued due to a protocol violation of noncompliance with study drug.

8.3.8.1.2.2 Adjudicated Non-APTC CV Events - Phase 3 Controlled Studies

The number and percentage of subjects who experienced adjudicated non-APTC CV events in each of the Phase 3 controlled studies and overall are summarized in Table 47.

Table 47 Adjudicated Non-APTC CV Events (Phase 3 Controlled Studies)

Study	Placebo % (n/N)	Febuxostat 40 mg % (n/N)	Febuxostat 80 mg % (n/N)	Febuxostat 120 mg % (n/N)	Febuxostat 240 mg % (n/N)	Febuxostat Total % (n/N)	Allopurinol % (n/N)
APEX	0.8 (1/134)	NE	1.5 (4/267)	1.1 (3/269)	0.8 (1/134)	1.2 (8/670)	0.4 (1/268)
FACT	NE	NE	0.8 (2/256)	2.0 (5/251)	NE	1.4 (7/507)	1.6 (4/253)
CONFIRMS	NE	1.3 (10/757)	1.2 (9/756)	NE	NE	1.3 (19/1513)	0.9 (7/756)
Total	**0.8 (1/134)**	**1.3 (10/757)**	**1.2 (15/1279)**	**1.5 (8/520)**	**0.8 (1/134)**	**1.3 (34/2690)**	**0.9 (12/1277)**
95% CI	**0.02-4.09**	**0.64-2.42**	**0.66-1.93**	**0.67-3.01**	**0.02-4.09**	**0.88-1.76**	**0.49-1.64**

NE = treatment/dose not evaluated.

The individual types of non-APTC CV events are summarized by treatment dose for the combined Phase 3 controlled studies in Table 48. The most common type of non-APTC CV event was arrhythmia with no evidence of ischemia. All subjects had underlying CV risk factors. Of the 15 arrhythmias reported in the Phase 3 controlled studies, 8 occurred in the CONFIRMS Study and were discussed previously. The remaining 7 arrhythmias were: supraventricular tachycardia (febuxostat 240 mg); bradycardia (allopurinol); a defibrillator discharge (febuxostat 80 mg; the subject had a pre-existing defibrillator implant); atrial fibrillation (1 on febuxostat 80 mg, 2 on febuxostat 120 mg, and 1 on allopurinol). All events of arrhythmias were SAEs, expect the atrial fibrillation in the allopurinol group. All of these subjects completed the study, except for the subject with bradycardia.

Table 48 Analyses of Subjects With Adjudicated Non-APTC CV Events (Phase 3 Controlled Studies)

Non-APTC CV Criterion	Placebo (N=134)	Febuxostat 40 mg (N=757)	Febuxostat 80 mg (N=1279)	Febuxostat 120 mg (N=520)	Febuxostat 240 mg (N=134)	Febuxostat Total (N=2690)	Allopurinol (N=1277)
All Non-APTC CV Events							
Number of Subjects	1	10	15	8	1	34	12
Rate (%)	0.75	1.32	1.17	1.54	0.75	1.26	0.94
95% CI[a]	0.019-4.088	0.635-2.416	0.658-1.927	0.666-3.009	0.019-4.088	0.877-1.762	0.486-1.636
Arrhythmia, No Evidence of Ischemia							
Number of Subjects	0	3	6	2	1	12	3
Rate (%)	0.00	0.40	0.47	0.38	0.75	0.45	0.23
95% CI[a]	0.000-2.715	0.082-1.154	0.172-1.018	0.047-1.382	0.019-4.088	0.231-0.778	0.048-0.685
Venous and Peripheral Arterial Vascular Thrombotic Events							
Number of Subjects	0	0	3	2	0	5	0
Rate (%)	0.00	0.00	0.23	0.38	0.00	0.19	0.00
95% CI[a]	0.000-2.715	0.000-0.486	0.048-0.684	0.047-1.382	0.000-2.715	0.060-0.433	0.000-0.288
Nonfatal Congestive Heart Failure							
Number of Subjects	0	2	0	1	0	3	1
Rate (%)	0.00	0.26	0.00	0.19	0.00	0.11	0.08
95% CI[a]	0.000-2.715	0.032-0.951	0.000-0.288	0.005-1.067	0.000-2.715	0.023-0.326	0.002-0.436
Angina							
Number of Subjects	1	2	0	0	0	2	0
Rate (%)	0.75	0.26	0.00	0.00	0.00	0.07	0.00
95% CI[a]	0.019-4.088	0.032-0.951	0.000-0.288	0.000-0.707	0.000-2.715	0.009-0.268	0.000-0.288

Studies included are APEX, FACT, and CONFIRMS.

a The confidence intervals are calculated based on binomial distribution.

Table 48 Analyses of Subjects With Adjudicated Non-APTC CV Events (Phase 3 Controlled Studies) (continued)

Non-APTC CV Criterion	Placebo (N=134)	Febuxostat 40 mg (N=757)	Febuxostat 80 mg (N=1279)	Febuxostat 120 mg (N=520)	Febuxostat 240 mg (N=134)	Febuxostat Total (N=2690)	Allopurinol (N=1277)
Coronary Revascularization							
Number of Subjects	0	1	2	2	0	5	4
Rate (%)	0.00	0.13	0.16	0.38	0.00	0.19	0.31
95% CI[a]	0.000-2.715	0.003-0.734	0.019-0.564	0.047-1.382	0.000-2.715	0.060-0.433	0.085-0.800
Transient Ischemic Attack							
Number of Subjects	0	1	1	0	0	2	1
Rate (%)	0.00	0.13	0.08	0.00	0.00	0.07	0.08
95% CI[a]	0.000-2.715	0.003-0.734	0.002-0.435	0.000-0.707	0.000-2.715	0.009-0.268	0.002-0.436
Cerebral Revascularization							
Number of Subjects	0	0	0	0	0	0	0
Rate (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00
95% CI[a]	0.000-2.715	0.000-0.486	0.000-0.288	0.000-0.707	0.000-2.715	0.000-0.137	0.000-0.288
Other Non-APTC CV Events							
Number of Subjects	0	1	3	1	0	5	3
Rate (%)	0.00	0.13	0.23	0.19	0.00	0.19	0.23
95% CI[a]	0.000-2.715	0.003-0.734	0.048-0.684	0.005-1.067	0.000-2.715	0.060-0.433	0.048-0.685

Studies included are APEX, FACT, and CONFIRMS.

a The confidence intervals are calculated based on binomial distribution.

8.3.8.1.3 Summary of Cardiovascular Events

Subjects enrolled in the febuxostat clinical studies were representative of the overall population of patients with hyperuricemia and gout as they had significant comorbidities and multiple CV risk factors. Almost all subjects (89%) in the Phase 3 controlled studies had at least one cardiovascular risk factor; 30% of subjects had at least three CV risk factors, a combination of comorbidities and life-style factors. The incidence of CV risk factors was similar across treatment groups.

During the Phase 3 controlled studies, the incidence of adjudicated APTC and non-APTC CV events was low across treatment groups and similar for the various doses of febuxostat and for allopurinol. No causal role for febuxostat in the occurrence of CV adverse effects has been identified in either the mechanism of action of febuxostat or results of studies in animal models of CV diseases.

8.3.8.2 Hepatic Effects - Phase 3 Controlled Studies

Liver function abnormalities were reported as an AE at the discretion of the investigator and as a result, different investigators appear to have reported similar changes in liver enzyme levels inconsistently. Therefore, the hepatic laboratory results for all subjects were reviewed for abnormal values and a summary of that review is provided in this section.

Alcohol usage is strongly associated with an increased risk of gout[74] and is known to elevate liver enzymes. The majority (67%) of subjects reported drinking alcohol.

In the Phase 3 controlled studies, the percentages of subjects with alanine transaminase (ALT) elevations ≥3xULN were higher in the febuxostat 40 mg, 80 mg, 120 mg groups than the febuxostat 240 mg, placebo, and allopurinol groups (Table 49). There was no difference across treatment groups in the incidence of ALT or AST elevations ≥5xULN.

ALT or AST elevations ≥10xULN occurred in a few subjects on the higher febuxostat doses (one subject each on febuxostat 120 mg and 240 mg) and allopurinol (three subjects). The event on febuxostat 240 mg (in the APEX Study) was associated with cholelithiasis and is discussed below. The other event on 120 mg (in the FACT Study) was a single spike in AST that was

greater than the subject's ALT and occurred after approximately 250 days of study treatment. An alternate etiology of viral hepatitis was provided by the investigator. The subject was discontinued from the study and the event resolved approximately two weeks after discontinuation. Of the three subjects on allopurinol, one subject, with a history of alcohol use, was discontinued due to the event. One subject had an acute rise in AST and ALT of nearly 20-fold early in the FACT Study, which resolved and the subject completed the study. This subject entered the long term EXCEL Study and was randomized to febuxostat with no recurrence of liver enzyme elevations. The remaining event on allopurinol occurred in the CONFIRMS study in a subject who reported a concurrent AE of hepatitis B. The subject completed the study and the hepatic enzyme values returned to normal approximately 61 days after the last dose of study drug.

Two subjects met the criteria of ≥3xULN ALT and/or AST concurrent with total bilirubin ≥2xULN, but these changes were not considered related to study drug because of other explanatory findings:

- One subject was a 61 year-old male who was on 240 mg febuxostat in the APEX Study. He had normal ALT, AST, and total bilirubin levels at baseline (ULN: 40 U/L, 40 U/L, and 1.2 mg/dL, respectively). His levels increased to 663 U/L ALT, 350 U/L AST, and 10.3 mg/dL total bilirubin by 107 days. His alkaline phosphatase level at baseline was 61 U/L (ULN: 125 U/L) and his value was 83 U/L on Day 107. The subject was diagnosed with cholelithiasis. He remained on study drug and his liver function test values returned to baseline. The subject completed the study.
- The other subject was a 61 year-old male who was on 300 mg allopurinol in the APEX Study. He had normal ALT, AST, and total bilirubin levels at baseline (ULN: 43 U/L, 36 U/L, and 1.2 mg/dL, respectively). His levels increased to 232 U/L ALT, 317 U/L AST, and 5.3 mg/dL total bilirubin by 114 days. His alkaline phosphatase level at baseline was 65 U/L (ULN: 125 IU/L) and his maximum value was 118 U/L on Day 114. The subject was diagnosed with cholelithiasis, and had a cholestectomy. He remained on

study drug and his liver function test values returned to within normal range. The subject completed the study.

Therefore, no subject met the Hy's Law criteria (ALT and/or AST >3xULN with a total bilirubin >2xULN without findings of cholestasis and no other explanation, such as viral hepatitis or preexisting liver damage.[75]

As noted above, subjects were discontinued from study drug at the investigator's discretion. The rates of discontinuations due to elevated liver function tests was 1.8%, 1.4%, 1.9%, and 0% for febuxostat 40 mg, 80 mg, 120 mg, and 240 mg compared to 0.9% for allopurinol.

In summary, most elevations in liver function tests were mild, asymptomatic, and either resolved with continued therapy or promptly returned to baseline following discontinuation of study drug. The rate and magnitude of enzyme elevations were generally similar between the febuxostat and allopurinol groups.

Table 49 Proportions of Subjects With Elevated Liver Function Tests Values (Phase 3 Controlled Studies)

	Placebo N=134	Febuxostat 40 mg N=757	Febuxostat 80 mg N=1279	Febuxostat 120 mg N=520	Febuxostat 240 mg N=134	Febuxostat Total N=2690	Allopurinol N=1277
	Number of Subjects With Measurements						
	N=129 n (%)	N=711[b] n (%)	N=1204 n (%)	N=506 n (%)	N=127 n (%)	N=2548 n (%)	N=1200 n (%)
ALT							
≥3 -<5 ×ULN	1 (<1)	20 (3)	36 (3)	23 (5)	1 (<1)	80 (3)	17 (1)
≥5 - <10 ×ULN	0	3 (<1)	3 (<1)	1 (<1)	1 (<1)	8 (<1)	4 (<1)
≥10×ULN	0	0	0	0	1 (<1)	1 (<1)	2 (<1)
AST							
≥3 - <5 ×ULN	0	7 (<1)	15 (1)	11 (2)	0	33 (1)	16 (1)
≥5 - <10 ×ULN	1 (<1)	3 (<1)	1 (<1)	1 (<1)	2 (2)	7 (<1)	5 (<1)
≥10×ULN	0	0	0	1 (<1)	0	1 (<1)	3 (<1)
ALT and AST Concurrently[a]							
≥3 ×ULN	0	8 (1)	10 (<1)	8 (2)	2 (2)	28 (1)	12 (1)
Total Bilirubin							
≥2.0 x ULN	1 (<1)	1 (<1)	3 (<1)	4 (<1)	2 (2)	10 (<1)	8 (<1)
ALT &/or AST ≥ 3xULN Concurrently with:							
Total bilirubin ≥2.0 x ULN	0	0	0	0	1 (<1)	1 (<1)	1 (<1)

Studies included are APEX, FACT, and CONFIRMS.
Note: Subjects may be included in more than 1 category.
Note: Studies allowed subject to enroll with ALT or AST 1.5×ULN.
a Subjects in this category are also accounted for in the ALT and AST rows above.
b N=710 for AST measurements and is the denominator for any calculations that include AST measurements.

8.3.8.3 Renal Adverse Events - Phase 3 Controlled Studies

This section summarizes AEs associated with the renal system for the overall study population, in contrast to Section 8.3.7, which evaluated the incidence of AEs across the subgroups of subjects by renal function.

The percentages of treatment-emergent renal AEs in the Phase 3 controlled studies were similar between the placebo, total febuxostat, and allopurinol groups (Table 50). Edema was the most commonly reported renal AE. These events were mild in nature and showed a modest dose-related trend across the febuxostat groups, with the highest incidence of edema in the febuxostat 240 mg group. Fewer subjects had edema with febuxostat 40 mg (1.2%) than febuxostat 80 mg (2.7%) and allopurinol (2.5%). The majority of the subjects with edema were receiving either NSAIDs and/or calcium channel blockers, drugs known to cause edema, and only one-third of these subjects actually received diuretic therapy. Additionally, essentially all of the subjects with edema had a history of significant cardiovascular disease.

Table 50 Percentages of Subjects With Renal Adverse Events (≥0.1% and ≥2 Subjects in Any Treatment Group) (Phase 3 Controlled Studies)

MedDRA High Level Term	Placebo (N=134) n (%)	Febuxostat 40 mg (N=757) n (%)	Febuxostat 80 mg (N=1279) n (%)	Febuxostat 120 mg (N=520) n (%)	Febuxostat 240 mg (N=134) n (%)	Febuxostat Total (N=2690) n (%)	Allopurinol (N=1277) n (%)
Total Subjects With ≥1 Adverse Event	**8 (6.0)**	**29 (3.8)**	**78 (6.1)**	**34 (6.5)**	**13 (9.7)**	**154 (5.7)**	**78 (6.1)**
Edema NEC	1 (0.7)	9 (1.2)	34 (2.7)	16 (3.1)	6 (4.5)	65 (2.4)	32 (2.5)
Renal Function Analyses	3 (2.2)	6 (0.8)	5 (0.4)	4 (0.8)	3 (2.2)	18 (0.7)	10 (0.8)
Renal Failure and Impairment	0	2 (0.3)	10 (0.8)	4 (0.8)	2 (1.5)	18 (0.7)	2 (0.2)
Urinalysis NEC	1 (0.7)	2 (0.3)	8 (0.6)	1 (0.2)	0	11 (0.4)	4 (0.3)
Renal Lithiasis	1 (0.7)	7 (0.9)	12 (0.9)	4 (0.8)	1 (0.7)	24 (0.9)	14 (1.1)
Renal Neoplasms	0	1 (0.1)	3 (0.2)	1 (0.2)	0	5 (0.2)	1 (<0.1)
Urinary Abnormalities	1 (0.7)	5 (0.7)	13 (1.0)	5 (1.0)	3 (2.2)	26 (1.0)	15 (1.2)
Urinary Tract Signs and Symptoms NEC	0	0	2 (0.2)	0	0	2 (<0.1)	3 (0.2)

Studies included are APEX, FACT, and CONFIRMS.
MedDRA = Medical Dictionary for Regulatory Activities; NEC = not elsewhere classified in MedDRA.

Evaluation of the renal laboratory test results shows that changes in renal laboratory tests were reported inconsistently by investigators such that they were coded as either an AE of renal function analysis or as renal failure and impairment. Therefore, the renal laboratory tests were reviewed for subjects who had a serum creatinine level that showed a >30% increase from baseline (last value prior to first dose of study drug) and was higher than the ULN. The incidences of subjects meeting these criteria across treatment groups were 7%, 3%, 3%, 5%, 6%, and 3% for the placebo, febuxostat 40 mg, 80 mg, 120 mg, 240 mg, and allopurinol groups, respectively.

Another analysis further evaluated serum creatinine by reviewing change from mean baseline value (within 30 days prior to first dose). A clinically meaningful change was defined as a serum creatinine increase ≥0.7 mg/dL with an absolute value ≥2 mg/dL. Again, based on this definition, the incidence of renal impairment was similar across treatment groups.

8.3.8.4 Rash - Phase 3 Controlled Studies

Rash is a known side effect of the only other XO inhibitor currently in use, allopurinol;[68] therefore, all rashes in the febuxostat clinical program were proactively identified and carefully evaluated.

In the combined Phase 3 controlled studies, 6% of subjects in the combined febuxostat groups and 6% in the allopurinol group experienced treatment-emergent rash AEs. None of these rash AEs were serious, and the majority were mild to moderate in severity. The most common types of rashes were dermatitis and eczema (2.2% and 3.3% in febuxostat and allopurinol groups) and rashes, eruptions and exanthems (2.0% and 1.3% in febuxostat and allopurinol groups). The percentage of subjects who discontinued due to a rash was low and comparable in the febuxostat and allopurinol groups (0.9% and 0.8%).

8.3.8.5 Drug Hypersensitivity - Phase 3 Controlled Studies

Two subjects experienced AEs coded to drug hypersensitivity during the Phase 3 controlled studies: one on febuxostat 80 mg and one on allopurinol.

The subject on febuxostat was a 50 year-old male enrolled in the FACT Study. He was hospitalized with an allergic reaction on Day 305 of the study. The subject started Aldomet for hypertension on Day 301 and developed the reaction five days later. The subject was discontinued from the study. The investigator considered the event related to the Aldomet and the subject recovered with discontinuation of the Aldomet.

The subject on allopurinol was a 36 year-old male enrolled in the CONFIRMS Study. He experienced an SAE of drug hypersensitivity following 43 days of dosing with allopurinol 300 mg QD. The subject reported redness and peeling of soles of his feet and the palms of his hands. He was evaluated by the investigator, who noted mild but definite desquamation of the skin with loss of pigmentation, describing it as an exfoliative rash. The SAE was severe in nature and resulted in discontinuation of study drug. It is unknown whether the subject had been previously exposed to allopurinol. The SAE was treated with dexamethasone and methylprednisolone and the event resolved 17 days later. The investigator determined that this event was definitely related to allopurinol.

8.3.8.6 Other Organ System Effects

A review of the safety data from both the Phase 3 controlled studies and the open-label, long-term studies for the gastrointestinal, hematological, and neurological systems, lipid metabolism, or thyroid did not identify any potential risk associated with febuxostat.

8.4 Safety in Open-Label Long-Term Extension Studies

The long-term extension studies, FOCUS and EXCEL, were both open-label and allowed switching treatments if needed to achieve a stable drug and dose that could maintain an sUA level between 3.0 mg/dL and 6.0 mg/dL. See Section 6.2 and Table 3 for brief descriptions of the study designs for these studies.

In order to compensate for substantial differences in duration of exposure among treatment groups, AEs, laboratory shifts, potentially clinically important (PCI), and liver function test (LFT) tables in the open-label, long-term extension studies are summarized by patient-years of exposure (PY).

Because subjects were allowed to switch treatment, a subject could have been counted in more than one treatment group. For subjects who switched from one treatment to another, laboratory evaluations or AEs were assigned to the treatment the subjects was receiving at the time of onset of the AE or at the evaluation. It is important to note that a subject may have been exposed to a different treatment and/or dose prior to the onset of the current AE. Approximately 60% of the allopurinol subjects in the EXCEL Study switched to febuxostat, leaving only a small number of subjects whose final stable treatment was allopurinol. Data from the open-label, long-term extension studies were summarized by treatment, but it was not intended for comparisons across treatments due to substantial imbalances in sample sizes, treatment duration differences, and protocol-allowed switching between treatments. Therefore, discussion in this document focuses on data for febuxostat total to evaluate long-term safety of febuxostat treatment.

Results by treatment group are also presented, however, meaningful comparisons between treatment groups are limited and should be interpreted with caution.

8.4.1 Exposure - Open-Label, Long-Term Extension Studies

In the 2 open-label, long-term extension studies, 1143 subjects received ≥1 dose of febuxostat, for a total of 2660.9 PY of febuxostat exposure. As previously described, per protocol, subjects had their treatment switched as needed based on sUA level, an AE, or at the discretion of the investigator.

A summary of treatment switches (between the initial and final treatment) is shown in Table 51. Ninety seven percent of subjects remained on some dose of febuxostat. Fifty-nine percent of subjects initially assigned to allopurinol switched to febuxostat, limiting the amount of allopurinol exposure available for comparison.

Table 51 Treatment Switches from Initial Treatment to Final Treatment (Open-Label, Long-Term Studies)

	Final Treatment			
	Febuxostat			
Initial Treatment	40 mg	80 mg	120 mg	Allopurinol
Febuxostat 80 mg (N=765)	8 (1%)	577 (75%)	174 (23%)	6 (<1%)
Febuxostat 120 mg (N=292)	0	54 (18%)	211 (72%)	27 (9%)
Allopurinol (N=145)	0	54 (37%)	32 (22%)	59 (41%)

Studies included are FOCUS and EXCEL.

Table 52 summarizes study drug exposure by treatment group. Since subjects may have received more than 1 treatment in these studies, the total number of subjects receiving each febuxostat regimen is higher than the total number of unique subjects receiving febuxostat.

Table 52 Summary of Exposure (Open-Label Long-Term Extension Studies)

	Febuxostat				
Extent of Exposure	40 mg	80 mg	120 mg	Total[a]	Allopurinol
Number of Subjects (n)	12	917	524	1143	178
Patient-Years of Exposure (PY)	37.7	1745.6	877.7	2660.9	172.2
Mean Exposure (days)	1146.4	695.3	611.8	850.3	353.4
Cumulative Exposure (n)					
≥6 months	10	635	366	1003	83
≥12 months	8	579	315	909	56
≥24 months	8	503	258	781	46
≥36 months	6	246	40	348	4
≥48 months	6	40	11	60	0
≥60 months	6	39	10	60	0

Studies included are FOCUS and EXCEL.

a A subject may be included in more than one treatment group if the subject switched treatment during the study. Therefore, the "Total" column reflects total patient-exposure to febuxostat regardless of dose.

8.4.2 Adverse Events - Open-Label, Long-Term Studies

The incidence of AEs during the long-term extension studies are shown by 100 PY in Table 53. The AEs reported for subjects receiving any dose of febuxostat during the Phase 3 controlled studies have been converted to per 100 PY and are included in this table to allow a comparison between short and long-term exposure.

Overall the rates of AEs in the long-term extension studies for febuxostat were similar to those in the Phase 3 controlled studies. Similarly, the types of AEs reported were also similar to those reported in the controlled studies, with no new AE reports of concern.

Table 53 Most Frequently Reported (≥5 Events per 100 PY) Treatment-Emergent Adverse Events (Open-Label, Long-Term Studies Compared to the Phase 3 Controlled Studies)

	Open-Label, Long-Term Extension Studies					Phase 3 Controlled Studies	
	Febuxostat				Allopurinol	Allopurinol	Febuxostat
MedDRA High Level Term	40 mg N=12 (PY=37.7)	80 mg N=917 (PY=1745.6)	120 mg N=524 (PY=877.7)	Total N=1143 (PY=2660.9)	N=178 (PY=172.2)	N=1277 (PY=670.9)	Total N=2690 (PY= 1346.0)
	Number of Treatment Emergent Events (Rates Per 100 PY)						
Total Number of Events	**103 (273.5)**	**4408 (252.5)**	**1930 (219.9)**	**6441 (242.1)**	**423 (245.6)**	**2411 (359.4)**	**4958 (368.4)**
Upper Respiratory Tract Infections	11 (29.2)	481 (27.6)	209 (23.8)	701 (26.3)	38 (22.1)	222 (33.1)	441 (32.8)
Musculoskeletal and Connective Tissue Signs and Symptoms	4 (10.6)	275 (15.8)	125 (14.2)	404 (15.2)	31 (18.0)	126 (18.8)	298 (22.1)
Joint Related Signs and Symptoms	1 (2.7)	172 (9.9)	83 (9.5)	256 (9.6)	14 (8.1)	93 (13.9)	216 (16.0)
Headaches NEC	0	136 (7.8)	65 (7.4)	201 (7.6)	10 (5.8)	78 (11.6)	138 (10.3)
Lower Respiratory Tract and Lung Infections	2 (5.3)	108 (6.2)	36 (4.1)	146 (5.5)	7 (4.1)	35 (5.2)	56 (4.2)
Vascular Hypertensive Disorders	3 (8.0)	86 (4.9)	50 (5.7)	139 (5.2)	7 (4.1)	38 (5.7)	76 (5.6)
Gastrointestinal Atonic and Hypomotility Disorders	0	33 (1.9)	25 (2.8)	58 (2.2)	9 (5.2)	36 (5.4)	52 (3.9)
Skin Injuries NEC	1 (2.7)	42 (2.4)	13 (1.5)	56 (2.1)	9 (5.2)	20 (3.0)	39 (2.9)

MedDRA = Medical Dictionary for Regulatory Activities; NEC = not elsewhere classified in MedDRA; PY = patient-years of exposure.
Note: Most frequent events include MedDRA High Level Terms with at least 5 events per 100 patient-years (prior to rounding) in either the febuxostat 80 mg, febuxostat 120 mg, or allopurinol treatment groups.

8.4.3 Deaths - Open-Label, Long-Term Extension Studies

Ten deaths occurred during the open-label, long-term extension studies, seven subjects died while on febuxostat 80 mg and three subjects died while on febuxostat 120 mg. Table 54 shows the AEs that led to death in the long-term extension studies, along with those in the controlled studies. The incidence per 100 PY in the long-term studies (0.38/100 PY) was similar to that observed in the Phase 3 controlled studies (0.45/100 PY) for the total febuxostat groups. There was no discernible pattern with respect to treatment duration and time of death.

Table 54 AEs Leading to Death by Subject Rate per 100-PY for Open-Label, Long-Term Studies Compared to the Phase 3 Controlled Studies

	Open-Label, Long-Term Extension Studies					Phase 3 Controlled Studies	
	Febuxostat				Allopurinol N=178 (PY=172.2)	Allopurinol N=1277 (PY=670.9)	Febuxostat Total N=2690 (PY=1346.0)
	40 mg N=12 (PY=37.7)	80 mg N=917 (PY=1745.6)	120 mg N=524 (PY=877.7)	Total N=1143 (PY=2660.9)			
Cause of Death	Number of Deaths (Rate per 100 PY)						
Total Deaths	0	7 (0.40)	3 (0.34)	10 (0.38)	0	3 (0.45)	6 (0.45)
Anaphylactic Reaction							1
Brain edema/Chronic obstructive pulmonary disease							1
Cancer, bile duct		1		1			
Cancer, metastatic colon		1		1			
CHF, Respiratory failure, cardio-respiratory arrest		1		1			
Colon cancer							1
Hypertensive heart disease						1	
Lung adenocarcinoma/ necrotizing pneumonia/sepsis						1	
Myocardial infarction[a]		3	2	5			
Retroperitoneal hemorrhage			1	1			1
Respiratory failure							1
Resp failure/anoxic encephalopathy							1
Sepsis		1		1			
Sudden death						1	

a One subject in the 80 mg group and one in the 120 mg group had an acute myocardial infarction.

8.4.4 Serious Adverse Events - Open-Label, Long-Term Extension Studies

The incidence of SAEs per 100 PY in the total febuxostat group was 10.3 events in the open-label, long-term studies compared to 10.1 events in the Phase 3 controlled studies (Table 55). Similar to the controlled studies, the most common SAEs per 100 PY in the total febuxostat group were ischemic coronary artery disorders and coronary artery disorders (NEC). The CV SAEs are discussed in more detail in Section 8.4.6. Overall the types of SAEs were similar when compared to the controlled studies. The safety profile of febuxostat did not change with long-term use.

8.4.5 Discontinuations Due to Adverse Event - Open-Label, Long-Term Extension

In the open-label, long-term extension studies, the incidence of AEs that led to discontinuation was 4.4 events/100 PY for the total febuxostat group compared to 22.0 events/100 PY in the Phase 3 controlled studies. This difference is representative of subjects self selecting to continue in an extension study. Similar to the controlled studies, the most common type of AE that led to discontinuation was liver function analyses.

For discontinuations due to AEs in the open-label, long-term extension studies, there was no apparent trend based on time of onset or type of event.

Table 55 Incidence of Treatment-Emergent Serious Adverse Events (>0.3 per 100 PY) (Open-Label, Long-Term Studies Compared to Phase 3 Controlled Studies)

	Open-Label, Long-Term Extension Studies					Phase 3 Controlled Studies	
	Febuxostat				Allopurinol N=178 (PY=172.2)	Allopurinol N=1277 (PY=670.9)	Febuxostat Total N=2690 (PY= 1346.0)
	40 mg N=12 (PY=37.7)	80 mg N=917 (PY=1745.6)	120 mg N=524 (PY=877.7)	Total N=1143 (PY=2660.9)			
MedDRA High Level Term	Number of Treatment-Emergent Events (Rates Per 100 PY)						
Total Events	**8 (21.2)**	**187 (10.7)**	**78 (8.9)**	**273 (10.3)**	**21 (12.2)**	**68 (10.1)**	**136 (10.1)**
Osteoarthropathies	0	4 (0.2)	9 (1.0)	13 (0.5)	0	2 (0.3)	1 (<0.1)
Ischemic Coronary Artery Disorders[a]	0	19 (1.1)	4 (0.5)	23 (0.9)	2 (1.2)	3 (0.4)	11 (0.8)
Coronary Artery Disorders NEC	0	14 (0.8)	6 (0.7)	20 (0.8)	1 (0.6)	6 (0.9)	4 (0.3)
Cholecystitis and Cholelithiasis	1 (2.7)	10 (0.6)	1 (0.1)	12 (0.5)	2 (1.2)	4 (0.6)	0
Lower Respiratory Tract and Lung Infections	2 (5.3)	9 (0.5)	3 (0.3)	14 (0.5)	0	4 (0.6)	3 (0.2)
Supraventricular Arrhythmias	0	7 (0.4)	3 (0.3)	10 (0.4)	1 (0.6)	0	6 (0.4)
Central Nervous System Haemorrhages and Cerebrovascular Accidents	1 (2.7)	6 (0.3)	2 (0.2)	9 (0.3)	0	1 (0.1)	2 (0.1)
Pulmonary Thrombotic and Embolic Conditions	0	5 (0.3)	0	5 (0.2)	1 (0.6)	0	2 (0.1)
Abdominal and Gastrointestinal Infections	0	4 (0.2)	3 (0.3)	7 (0.3)	2 (1.2)	4 (0.6)	3 (0.2)
Heart Failure NEC	0	4 (0.2)	4 (0.5)	8 (0.3)	1 (0.6)	1 (0.1)	8 (0.6)
Intervertebral Disc Disorders	0	0	3 (0.3)	3 (0.1)	1 (0.6)	0	0
Spine and Neck Deformities	1 (2.7)	1 (<0.1)	0	2 (<0.1)	2 (1.2)	0	1 (<0.1)

MedDRA = Medical Dictionary for Regulatory Activities; NEC = not elsewhere classified in MedDRA.
Note: The table includes events that occurred in >0.3% of subjects in either the febuxostat 80 mg or febuxostat 120 mg groups.
a Preferred Terms: acute myocardial infarction, angina pectoris, angina unstable, myocardial infarction, myocardial ischemia.

8.4.6 Cardiovascular Events - Open-Label, Long-Term Studies

8.4.6.1 Adjudicated APTC Events - Open-Label, Long-Term Studies

The adjudication process for APTC events in the open-label, long-term extension studies, FOCUS and EXCEL, was done retrospectively as described for the APEX and FACT Studies in Section 8.3.8.1.

The incidence of APTC events in the open-label, long-term studies for all febuxostat subjects was 1.01 events per 100 PY compared to 0.74 events per 100 PY in the Phase 3 controlled studies (Table 56). There was no discernible pattern in time to onset of the events. The incidence of the individual type of APTC event for febuxostat-treated subjects regardless of dose was: CV death 0.26 events/100 PY; nonfatal myocardial infarction 0.41 events/100 PY; and nonfatal stroke 0.34 events/100 PY.

Table 56 Analyses of Subjects With Adjudicated APTC Events by Patient-Years of Exposure (Open-Label, Long-Term Extension Studies Compared with the Phase 3 Controlled Studies)

	Open-Label, Long-Term Extension Studies					Phase 3 Controlled Studies	
	Febuxostat				Allopurinol	Allopurinol	Febuxostat
	40 mg (N=12) (PY=37.7)	80 mg (N=917) (PY=1745.6)	120 mg (N=524) (PY=877.7)	Total (N=1143) (PY=2660.9)	(N=178) (PY=172.2)	(N=1277) (PY=670.9)	Total (N=2690) (PY=1346.0)
All APTC Events							
Number of Subjects	1	17	9	27	1	4	10
Rate per 100 PY	2.66	0.97	1.03	1.01	0.58	0.60	0.74
95% CI[a]	0.067-14.793	0.567-1.559	0.469-1.947	0.669-1.476	0.015-3.235	0.162-1.526	0.356-1.366
Cardiovascular Death							
Number of Subjects	0	4	3	7	0	2	3
Rate per 100 PY	0.00	0.23	0.34	0.26	0.00	0.30	0.22
95% CI[a]	0.000-9.794	0.062-0.587	0.070-0.999	0.106-0.542	0.000-2.142	0.036-1.077	0.046-0.651
Nonfatal Myocardial Infarction							
Number of Subjects	0	8	3	11	1	2	5
Rate per 100 PY	0.00	0.46	0.34	0.41	0.58	0.30	0.37
95% CI[a]	0.000-9.794	0.198-0.903	0.070-0.999	0.206-0.740	0.015-3.235	0.036-1.077	0.121-0.867
Nonfatal Stroke							
Number of Subjects	1	5	3	9	0	0	2
Rate per 100 PY	2.66	0.29	0.34	0.34	0.00	0.00	0.15
95% CI[a]	0.067-14.793	0.093-0.668	0.070-0.999	0.155-0.642	0.000-2.142	0.000-0.550	0.018-0.537

APTC=Antiplatelet Trialists' Collaboration; CI=confidence interval; PY=patient-years of exposure.

a The confidence intervals are calculated based on Poisson distribution.

8.4.6.2 Adjudicated Non-APTC CV Events in Open-Label, Long-Term Extension Studies

The rate per 100 PY of non-APTC CV events during the long-term studies was lower than during the Phase 3 controlled studies with febuxostat (1.58 vs 2.53 events/100 PY in febuxostat total) (Table 57).

Similar to the subjects with APTC events, all subjects who experienced a non-APTC CV event had extensive CV medical history.

Table 57 Analyses of Subjects With Adjudicated Non-APTC CV Events by Patient-Years of Exposure (Open-Label, Long-Term Extension Studies Compared with Phase 3 Controlled Studies)

	Open-Label, Long-Term Extension Studies					Phase 3 Controlled Studies	
	Febuxostat				Allopurinol	Allopurinol	Febuxostat
	40 mg (N=12) (PY=37.7)	80 mg (N=917) (PY=1745.6)	120 mg (N=524) (PY=877.7)	Total (N=1143) (PY=2660.9)	(N=178) (PY=172.2)	(N=1277) (PY=670.9)	Total (N=2690) (PY=1346.0)
All Non-APTC CV Events							
Number of Subjects	0	31	11	42	4	12	34
Rate per 100 PY	0.00	1.78	1.25	1.58	2.32	1.79	2.53
95% CI[a]	0.000-9.794	1.207-2.521	0.626-2.242	1.138-2.134	0.633-5.947	0.924-3.124	1.749-3.530
Arrhythmia, No Evidence of Ischemia							
Number of Subjects	0	6	3	9	1	3	12
Rate per 100 PY	0.00	0.34	0.34	0.34	0.58	0.45	0.89
95% CI[a]	0.000-9.794	0.126-0.748	0.070-0.999	0.155-0.642	0.015-3.235	0.092-1.307	0.461-1.557
Venous and Peripheral Arterial Vascular Thrombotic Events							
Number of Subjects	0	5	0	5	1	0	5
Rate per 100 PY	0.00	0.29	0.00	0.19	0.58	0.00	0.37
95% CI[a]	0.000-9.794	0.093-0.668	0.000-0.420	0.061-0.439	0.015-3.235	0.000-0.550	0.121-0.867
Non-Fatal Congestive Heart Failure							
Number of Subjects	0	3	2	5	0	1	3
Rate per 100 PY	0.00	0.17	0.23	0.19	0.00	0.15	0.22
95% CI[a]	0.000-9.794	0.035-0.502	0.028-0.823	0.061-0.439	0.000-2.142	0.004-0.830	0.046-0.651
Angina							
Number of Subjects	0	0	0	0	0	0	2
Rate per 100 PY	0.00	0.00	0.00	0.00	0.00	0.00	0.15
95% CI[a]	0.000-9.794	0.000-0.211	0.000-0.420	0.000-0.139	0.000-2.142	0.000-0.550	0.018-0.537
Coronary Revascularization							
Number of Subjects	0	10	5	15	2	4	5
Rate per 100 PY	0.00	0.57	0.57	0.56	1.16	0.60	0.37
95% CI[a]	0.000-9.794	0.275-1.054	0.185-1.329	0.316-0.930	0.141-4.195	0.162-1.526	0.121-0.867
Transient Ischemic Attack							
Number of Subjects	0	0	0	0	0	1	2
Rate per 100 PY	0.00	0.00	0.00	0.00	0.00	0.15	0.15
95% CI[a]	0.000-9.794	0.000-0.211	0.000-0.420	0.000-0.139	0.000-2.142	0.004-0.830	0.018-0.537

APTC=Antiplatelet Trialists' Collaboration; CI=confidence interval; PY=patient-years of exposure.

a The confidence intervals are calculated based on Poisson distribution.

Table 57 Analyses of Subjects With Adjudicated Non-APTC CV Events by Patient-Years of Exposure (Open-Label, Long Term Extension Studies Compared with Phase 3 Controlled Studies) (continued)

	Open-Label, Long-Term Extension Studies					Phase 3 Controlled Studies	
	Febuxostat				Allopurinol (N=178) (PY=172.2)	Allopurinol (N=1277) (PY=670.9)	Febuxostat
	40 mg (N=12) (PY=37.7)	80 mg (N=917) (PY=1745.6)	120 mg (N=524) (PY=877.7)	Total (N=1143) (PY=2660.9)			Total (N=2690) (PY=1346.0)
Cerebral Revascularization							
Number of Subjects	0	2	0	2	0	0	0
Rate per 100 PY	0.00	0.11	0.00	0.08	0.00	0.00	0.00
95% CI[a]	0.000-9.794	0.014-0.414	0.000-0.420	0.009-0.272	0.000-2.142	0.000-0.550	0.000-0.274
Other Non-APTC CV Events							
Number of Subjects	0	5	1	6	0	3	5
Rate per 100 PY	0.00	0.29	0.11	0.23	0.00	0.45	0.37
95% CI[a]	0.000-9.794	0.093-0.668	0.003-0.635	0.083-0.491	0.000-2.142	0.092-1.307	0.121-0.867

APTC=Antiplatelet Trialists' Collaboration; CI=confidence interval; PY=patient-years of exposure.

a The confidence intervals are calculated based on Poisson distribution.

8.4.7 Hepatic Effects - Open-Label, Long-Term Extension Studies

A small number of subjects experienced liver function test elevations in the open-label, long-term studies (Table 58). Similar to the Phase 3 controlled studies, liver function abnormalities was the most frequently reported AE leading to discontinuation in the total febuxostat group (0.6 events/100 PY).

Similar to the Phase 3 controlled studies, few subjects experienced ALT or AST ≥10 x ULN (two subjects each on febuxostat 80 mg and 120 mg). One of the subjects on febuxostat 80 mg reported a concurrent event of choleolithiasis, and is discussed below. The other subject, who had a history of hepatitis B and illicit drug use, experienced an elevation after more than 390 days of study drug. Both subjects were discontinued due to the event. Of the two subjects on febuxostat 120 mg, one experienced AST elevations greater than ALT, which is consistent with alcohol binge drinking; this subject completed the study. The other subject, who had a history of gallstones, experienced a late rise in ALT and AST after approximately 1043 days of study drug. The subject underwent a cholecystectomy that resulted in normalization of liver enzymes, and discontinued study drug due to the event.

Two subjects, both in the febuxostat 80 mg group, experienced concurrent elevations of AST and/or ALT ≥3xULN and total bilirubin ≥2xULN:

- One subject was a 73 year-old female who was on 80 mg febuxostat in the FOCUS Study. She had normal ALT, AST, and total bilirubin levels at baseline (ULN: 40 U/L, 38 U/L, and 1.3 mg/dL, respectively). Her levels increased to 313 U/L ALT, 240 U/L AST, and 7.4 mg/dL total bilirubin on Day 44 of treatment. Her alkaline phosphatase level was 123 U/L at baseline (ULN: 117 U/L) and 227 U/L on Day 44. The subject was diagnosed with bile duct stones and discontinued study drug. Her liver function test values returned to normal by Day 175.
- The other subject was a 57 year-old male who was on 80 mg febuxostat in the EXCEL Study. He had normal ALT, AST, and total bilirubin levels at baseline (ULN: 43 U/L, 36 U/L, and 1.2 mg/dL, respectively). His levels increased to 301 U/L ALT, 148 U/L

AST, and 5.7 mg/dL total bilirubin by Day 1330. His alkaline phosphatase level was 66 U/L at baseline (ULN: 131 U/L) and 313 U/L (ULN: 125 U/L) on Day 1330. The subject was diagnosed with bile duct cancer and subsequently died from the disease.

No subject met Hy's law criteria (ALT and/or AST >3xULN with a total bilirubin >2xULN without findings of cholestasis and no other explanation, such as viral hepatitis, pre-existing liver damage),[75] and no subject experienced a drug-induced liver injury.

Table 58 Proportions of Subjects With Elevated Liver Function Tests Values (Open-Label, Long-Term Extension Studies)

Hepatic Chemistry Parameter Elevation Criterion	Open-Label, Long-Term Extension Study				
	Febuxostat				Allopurinol
	40 mg (N=12) (PY=37.7)	80 mg (N=917) (PY=1745.6)	120 mg (N=524) (PY=877.7)	Total (N=1143) (PY = 2660.9)	(N=178) (PY=172.2)
Subjects With Results	**n=12 (PY=37.7)**	**n=898 (PY=1744.8)**	**n=505 (PY=876.7)**	**n=1120 (PY=2659.8)**	**n=173 (PY=172.0)**
Number of Treatment Emergent Subjects (Rates Per 100 PY)					
ALT					
≥3 - <5 ×ULN	1 (2.7)	31 (1.8)	17 (1.9)	46 (1.7)	2 (1.2)
≥5 - <10 ×ULN	0	3 (0.2)	2 (0.2)	5 (0.2)	2 (1.2)
≥10×ULN	0	2 (0.1)	1 (0.1)	3 (0.1)	0
AST					
≥3 -<5 ×ULN	0	16 (0.9)	13 (1.5)	27 (1.0)	0
≥5 - <10 ×ULN	0	3 (0.2)	1 (0.1)	4 (0.2)	3 (1.7)
≥10×ULN	0	1 (0.1)	1 (0.1)	2 (0.1)	0
ALT and AST Concurrently[a]					
≥3 ×ULN	0	13 (0.7)	9 (1.0)	21 (0.8)	3 (1.7)
Total Bilirubin					
≥2.0 xULN	0	7 (0.4)	2 (0.2)	9 (0.3)	0
ALT &/or AST ≥ 3xULN Concurrently with:					
Total bilirubin ≥2.0xULN	0	2 (0.1)	0	2 (0.1)	0

PY = patient-years for subjects with tests; Rate = rate adjusted by exposure.

Note: Subjects in the open-label, long-term extension studies may be counted in more than 1 treatment group and may have experienced an LFT elevation on more than 1 treatment.

a Subjects in this category are also accounted for in the ALT and AST rows above.

8.4.8 Renal Effects - Open-Label, Long-Term Extension

In the open-label, long-term extension studies, the overall incidences of subjects with treatment-emergent renal AEs per 100 PY were 6.5 subjects in the febuxostat total group compared to 11.4 subjects in the Phase 3 controlled studies. The most frequent renal AEs are presented in Table 59. These events were similar to those reported in the Phase 3 controlled studies.

Table 59 Most Frequent Renal AEs (≥1 Subject per 100 PY) (Open-Label Long-Term Extension Studies Compared to Phase 3 Controlled Studies)

	Open-Label, Long-Term Extension Studies					Phase 3 Controlled Studies
	Febuxostat				Allopurinol	Febuxostat
MedDRA High Level Term	40 mg (N=12) (PY=37.7)	80 mg (N=917) (PY=1745.6)	120 mg (N=524) (PY=877.7)	Total (N=1143) (PY=2660.9)	(N=178) (PY=172.2)	Total (N=2690) (PY=1346.0)
Number of Subjects With AEs (Rate per 100 PY)						
Total Subjects With ≥ 1 AE	**2 (5.3)**	**129 (7.4)**	**46 (5.2)**	**172 (6.5)**	**10 (5.8)**	**154 (11.4)**
Edema NEC	0	58 (3.3)	19 (2.2)	77 (2.9)	3 (1.7)	65 (4.8)
Renal Lithiasis	1 (2.7)	24 (1.4)	12 (1.4)	36 (1.4)	3 (1.7)	24 (1.8)
Urinary Abnormalities	0	15 (0.9)	15 (1.7)	30 (1.1)	2 (1.2)	26 (1.9)
Renal Function Analyses	1 (2.7)	16 (0.9)	5 (0.6)	21 (0.8)	2 (1.2)	18 (1.3)
Renal Neoplasms	0	5 (0.3)	1 (0.1)	6 (0.2)	3 (1.7)	5 (0.4)

MedDRA = Medical Dictionary for Regulatory Activities; NEC = not elsewhere classified in MedDRA; PY = patient-years of exposure.
Note: Treatment and dose at the time of the adverse event.

A review of the renal laboratory results determined that the incidence of clinically meaningful changes were similar across treatment groups. The number of subjects per 100 PY who had an increase in serum creatinine that was >30% of baseline and above ULN was 2.7, 5.0, 3.9, and 4.1 for febuxostat 40 mg, 80 mg and 120 mg compared to allopurinol.

8.4.9 Rash - Open-Label, Long-Term Extension Studies

The number of subjects with rash AEs per 100 PY was 6.0 in the febuxostat total group during the long-term extension studies. None of these rash AEs were serious, and the majority of them were mild to moderate in severity. The most common types of rash in the febuxostat total group

were dermatitis and eczema (2.7 subjects/100 PY) and rashes, eruptions and exanthems (1.7 subjects/100 PY).

Few subjects who experienced a rash discontinued the study due to the event. The number of discontinuations per 100 PY was 0.2 subjects for febuxostat and 1.2 subjects for allopurinol.

8.4.10 Drug Hypersensitivity - Open-Label, Long-Term Extension Studies

Three febuxostat subjects and one allopurinol subject had reactions that were coded to drug hypersensitivity. All four subjects were taking concomitant medications and the hypersensitivity reaction was considered related to a concomitant medication, not febuxostat: provochol (subject on febuxostat 80 mg); cephalexin (subject on febuxostat 120 mg); augmentin (2 subjects on febuxostat 120 mg); and atenolol (allopurinol subject).

8.5 Other Safety Evaluations

8.5.1 Clinical Laboratory Evaluations

Febuxostat 40 mg and febuxostat 80 mg doses had no clinically important affect on any hematology, chemistry, thyroid, or urinalysis parameters during the clinical studies.

See Section 8.3.8.2 for a discussion of liver function tests and Section 8.3.8.3 for a discussion of renal-related laboratory (creatinine) results in the Phase 3 controlled studies.

Due to the mechanism of action of febuxostat, inhibition of xanthine oxidase would be expected to increase xanthine or/and hypoxanthine levels, and raise concerns for the potential of xanthine crystal formation. To investigate this issue, serum and urine xanthine and hypoxanthine assays were performed in 6 Phase 1 multiple-dose studies, enrolling a total of 293 subjects exposed to febuxostat. Urine sediment analyses for xanthine crystals were performed by x-ray diffraction and Fourier transform infrared spectroscopy in 2 Phase 1 studies and in the Phase 2 Dose-Ranging Study and the FOCUS Study. Xanthine crystals were not found in the urine of subjects treated with up to 300 mg febuxostat in Phase 1 and up to 120 mg in Phase 2 clinical studies.

No xanthine stones were reported in the Phase 3 controlled studies. In addition, all subjects with persistent hematuria in those studies were evaluated and no case warranted further workup.

8.5.2 Vital Signs, Physical Findings, and Other Observations Related to Safety

In the combined Phase 3 controlled studies, febuxostat 40 mg and febuxostat 80 mg had no clinically relevant effect on the vital signs of diastolic (DBP) and systolic blood pressure (SBP) and pulse.

To assess a potential antihypertensive effect of febuxostat, a retrospective analysis was performed on the Phase 3 controlled studies dataset. Subjects who had a SBP ≥160 mmHg or DBP ≥95 mmHg at baseline and who were not on antihypertensive drugs at baseline were included in this analysis (N=206). Results of this analysis showed a modest decrease in SBP and DBP with all treatments. Based on this analysis, no adverse change was observed with febuxostat.

In the long-term extension studies, febuxostat 80 mg and febuxostat 120 mg doses had no clinically relevant effect on the vital signs of diastolic and systolic blood pressure and pulse. There were no specific patterns and no dose-response effect with febuxostat.

8.6 General Safety Information

8.6.1 Phase 1 Studies

Twenty-five Phase 1 studies providing febuxostat safety data have been completed. Eleven Phase 1 studies administered single doses of febuxostat 20 mg, 40 mg, 80 mg, and 120 mg to 304 healthy subjects and subjects. Fourteen Phase 1 studies administered multiple QD doses of febuxostat ranging from 10 mg to 300 mg to 535 healthy subjects and subjects. Each of the Phase 1 studies was conducted in healthy subjects, with the exception of 2 studies that evaluated the PK and PD of febuxostat in subjects with: 1) varying degrees of renal impairment; and 2) varying degrees of hepatic impairment.

Among the 839 subjects who received at least 1 dose of febuxostat in the Phase 1 studies, 425 (51%) reported at least 1 treatment-emergent AEs. One subject experienced an SAE (vaginal laceration) that occurred during the washout period between regimens (after receiving a single dose of febuxostat 80 mg and hydrochlorothiazide 50 mg). The event was considered not related to study drug by the investigator, who indicated an alternative etiology of sexual intercourse.

The 10 most commonly reported treatment-emergent AEs during febuxostat dosing included the following MedDRA preferred terms: headache, nausea, dizziness, feeling hot, diarrhea, fatigue, loose stools, constipation, back pain, and dyspepsia

8.6.2 Phase 2 Dose-Ranging Study

Safety data from the shorter (28-day) Phase 2 Dose Ranging Study were not integrated with safety data from the Phase 3 controlled and are presented here.

The placebo-controlled study enrolled 153 subjects randomized across four treatment groups. The number of subjects who experienced AEs was similar among the placebo and the febuxostat treatment groups (50% placebo, 54% febuxostat 40 mg, 58% febuxostat 80 mg and 50% febuxostat 120 mg). Diarrhea was observed more frequently in the febuxostat 80 mg treatment group (20%) compared to the placebo, febuxostat 40 mg and febuxostat 120 mg treatment groups (11%, 3% and 11%, respectively). The majority of the AEs reported were mild or moderate in severity.

Three subjects (1 febuxostat 80 mg and 2 febuxostat 120 mg) reported SAEs, which were: 1) pneumonia, delirium and Guillain-Barré Syndrome; 2) back pain; and 3) suicide attempt. Six subjects (1 placebo, 1 febuxostat 40 mg, 2 febuxostat 80 mg and 2 febuxostat 120 mg) discontinued due to AEs, including diarrhea, gastrointestinal disorder, liver function test abnormality, delirium, increased creatinine, suicide attempt and angioedema.

Mean changes in hematology and chemistry variables were small and not considered clinically significant. Four of 8 subjects who had increases in hepatic values to >3xULN first observed on study drug treatment Day 1 (after 2 weeks of colchicine prophylaxis and prior to the start of febuxostat dosing). The increase in hepatic values for the other 4 subjects was first observed on Day 14 after 2 weeks of febuxostat/colchicine coadministration. All hepatic values returned to within normal limits by Day 28 or on follow-up laboratory measurements.

Results of other safety analyses demonstrated no clinically significant changes in ECGs or vital signs.

8.6.3 Drug-Drug Interactions

Subgroup analyses were performed on data from the combined Phase 3 controlled studies for the following concomitant medications: NSAIDs/cyclooxygenase -2 (COX-2) inhibitors; colchicine; aspirin; nitrates; angiotensin-converting enzyme (ACE) inhibitors; beta-blockers; HMGCoA-reductase inhibitors; insulin, acetaminophen, corticosteroids, warfarin, thiazides, and calcium channel blockers.

The clinical experience supports the lack of clinically relevant drug interactions predicted by the Phase 1 drug-drug interaction studies. No febuxostat dose adjustment is required based upon drug-drug interactions.

8.6.4 Electrocardiogram Evaluations

The effect of febuxostat on QTc intervals was evaluated in a Phase 1 study, which was discussed in Section 5.3.2. Febuxostat in doses up to 300 mg daily, at steady state, did not cause prolongation of the QTc interval in healthy subjects.

The effect on ECGs when febuxostat was given to subjects with gout was examined in a subset of subjects enrolled in the APEX Study. Each subject enrolled at a site that participated in the PK/PD substudy had electrocardiograms (ECGs) 15 minute apart at baseline (Day-1) and the end of the treatment period (Day 28). The proportions of subjects with a QTcF 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 QTcF interval.

8.7 Safety Discussion and Conclusions

Febuxostat was well tolerated in the clinical studies, which included 4072 subjects who received at least 1 dose of febuxostat, ranging from 10 mg to 300 mg. The recommended doses of 40 mg and 80 mg were evaluated in 2757 subjects with hyperuricemia and gout in Phase 2 and 3, placebo- or active-controlled studies. The demographic and baseline characteristics of these subjects were representative of subjects in the general population who require treatment of hyperuricemia and gout.

No clinically meaningful differences were observed in the incidence of AEs between the proposed doses of febuxostat 40 mg and 80 mg. The safety profiles of those febuxostat doses were similar to allopurinol. Febuxostat was well-tolerated in subjects with gout regardless of their renal function status. There was a small increase in AEs across treatment groups, including allopurinol, in subjects with moderate renal impairment compared to subjects with normal renal function. No serious drug-induced liver injury occurred during the study and no subject met the Hy's law criteria for liver damage. Febuxostat caused no serious cutaneous adverse reaction, while one subject experienced a serious hypersensitivity reaction to allopurinol.

The potential for CV risk was thoroughly reviewed. Although CV events were numerically low during the studies, there was an imbalance in the rates of events for febuxostat 80 mg and 120 mg compared to allopurinol in the combined APEX and FACT studies (N=1832). The imbalance was not seen in the CONFIRMS Study, which included a larger sample size (N=2269) and a more robust evaluation of the potential CV risk via a prospective adjudication process. No causal role for febuxostat in the occurrence of CV adverse effects has been identified in either the mechanism of action of febuxostat or results of studies in animal models of CV diseases.

9 Dose Recommendations

Based on the optimal risk-benefit balance, febuxostat 40 mg and 80 mg doses are both recommended for approval to allow clinicians individualized dosing options. The 80 mg dose is more effective in subjects with more severe disease as defined by the presence of tophi or higher sUA levels. The efficacy of both doses in reducing sUA levels to <6.0 mg/dL has been shown to be reproducible in randomized, controlled studies.

10 Postmarketing Commitments

The Phase 3 program has established the efficacy of febuxostat in reducing sUA to <6.0 mg/dL, a level when maintained is associated with reduction in gout flares and tophi resolution. To further evaluate the impact on the clinical manifestations of gout, Takeda has committed to conduct a long-term Phase 4 study. This will include treatment groups for febuxostat and allopurinol in patients with gout.

Xanthine oxidase inhibitors have been reported to increase concentrations of theophylline. Takeda has agreed to conduct a postmarketing Phase 1 drug-drug interaction study of the effect of multiple doses of febuxostat on the pharmacokinetics of theophylline. Product labeling will contraindicate use with theophylline until this study is completed.

Appropriate warnings and precautions will be included in the package insert to inform clinicians of the potential risks associated with the use of febuxostat. A comprehensive postmarketing pharmacovigilance plan for febuxostat has been designed to systematically collect, analyze, understand, and communicate safety information regarding the risk-benefit profile of febuxostat in a broader postmarketing setting. This will be accomplished through communication and education strategies applied to manage the potential risks noted from the preclinical and clinical data.

11 Benefits and Risks of Febuxostat

11.1 Unmet Medical Need

Gout is a progressive and debilitating disease associated with multiple comorbid conditions. Gout is caused by deposition of urate crystals in joints and parenchymal organs and the clinical manifestations, such as flares and tophi, are a direct result from these crystals. Management of gout and prevention of flares and tophi resolution are accomplished by maintaining sUA <6.0 mg/dL.

Current treatment options are limited. The most commonly prescribed therapy is allopurinol, which is a purine XO inhibitor that lacks enzyme specificity. Allopurinol is typically used at 300 mg QD, with a lower dose recommended for patients with renal impairment. Recent studies have shown that less than half of gout patients treated with allopurinol (typically 300 mg) achieve the level of sUA needed for effective management of the disease. Other limitations (drug interactions) or safety concerns (hypersensitivity reactions) also limit the utility of allopurinol. Allopurinol has a long history of use, but had not been studied rigorously in adequate and well-controlled studies. In addition, there are limited data from controlled clinical studies available to support higher dosing for allopurinol. When weighing the benefits and risks of therapeutic options, it is important to consider all relevant information. This required careful

consideration not only of the product under review, but also of the potential alternative treatments.

The febuxostat clinical program thoroughly studied more than 4000 subjects and demonstrates that febuxostat provides clear benefits for patients with hyperuricemia and gout. The development program included subjects representative of the general gout population who have a wide range of comorbid conditions (eg, multiple CV risk factors, renal impairment, obesity, diabetes, and hyperlipidemia).

11.2 Benefits

Reduction of sUA

Febuxostat has been proven effective in lowering and maintaining sUA <6.0 mg/dL. Achieving and maintaining a sUA level of <6.0 mg/dL is accompanied by reduction in gout flares and resolution of tophi, the clinical manifestations of gout. Febuxostat 40 mg has similar effectiveness in reduction of sUA as allopurinol.

Febuxostat 80 mg had statistically significantly greater proportions of subjects with sUA<6.0 mg/dL at the final study visit than the allopurinol group in all Phase 3 randomized controlled studies. This difference in the absolute rate ranging from 25%-38% for febuxostat 80 mg over allopurinol clearly establishes the added benefit of febuxostat 80 mg compared to allopurinol. Febuxostat 80 mg also demonstrates a therapeutic advantage over febuxostat 40 mg (20%-22% absolute difference in response rates). In addition, febuxostat 80 mg was effective in subjects with more severe disease, such as higher sUA levels or the presence of tophi.

Treatment Option for Patients with Comorbid Conditions

A high percentage of gout patients have some degree of renal impairment. Febuxostat 40 mg and 80 mg were effective in subjects with mild-to-moderate renal impairment. The safety profile among subjects with moderate renal impairment was similar to those for subjects with normal or mildly impaired renal function. As a result, there is no dose adjustment required with febuxostat. This is in contrast to allopurinol, which requires dose reduction to decrease potential adverse events in patients with renal impairment.

Patients with gout have multiple comorbidities requiring a range of medications raising concerns related to drug-drug interactions. Febuxostat has shown no significant drug interactions with commonly used drugs and can safely be administered concurrently with a wide variety of drugs.

Lack of Severe Skin Reactions

No serious skin reactions occurred in febuxostat-treated subjects. There was no hypersensitivity reaction associated with febuxostat. Allopurinol is known to have very serious skin reactions (AHS) with potentially fatal outcomes. One case of AHS in a subject on allopurinol was reported in the febuxostat clinical program.

11.3 Potential Risks

Cardiovascular Safety

A thorough evaluation of a potential CV risk was undertaken. These steps included a detailed review of CV (APTC) endpoints in the APEX and FACT Studies. In these two initial Phase 3 studies, APTC events were numerically low, but there was an imbalance in the rate of events for febuxostat 80 mg and 120 mg compared to allopurinol or placebo. For both studies, the APTC evaluation process was done as part of a safety review after the studies were completed. To address this issue more fully, a new randomized, controlled study (CONFIRMS) was developed in which CV endpoint determination was defined prospectively.

The numerical imbalance was not seen in this larger Phase 3 study. In the CONFIRMS Study, there was no evidence of CV risk for febuxostat 40 mg; the incidence rates of adjudicated APTC events were low and similar for febuxostat 80 mg and allopurinol. No mechanism that would associate febuxostat with detrimental CV effects in humans was observed in nonclinical studies. In addition, febuxostat showed no untoward effect on blood pressure in our clinical studies.

Hepatic Effects

Hepatic effects were generally mild and the percentage of subjects with transaminase elevations ≥3 xULN was low and similar for febuxostat- and allopurinol-treated subjects. No dose response

was seen across febuxostat treatment groups. However, as with allopurinol, periodic liver function tests are recommended during therapy.

Treatment-Initiated Gout Flares

Paradoxical gout flares are an unavoidable consequence of urate-lowering therapy. The greater the magnitude of the reduction of sUA, the greater the incidence of gout flare. Therefore, more potent agents are associated with more treatment-initiated flares. It is recommended that with initiation of any ULT, such as febuxostat, patients should receive concomitant prophylaxis (eg, colchicine or nonsteroidal anti-inflammatory drugs [NSAIDs]) for gout flares.

12 Summary and Conclusions

Febuxostat is a potent, nonpurine, selective inhibitor of XO, which has been shown to be effective in reducing and maintaining sUA <6.0 mg/dL at doses of 40 mg and 80 mg. Maintaining these sUA levels is associated with the clinical benefits of tophi resolution and reduction in gout flare. Febuxostat 40 mg and 80 mg provide an effective treatment option for patients with hyperuricemia and gout. Based on the clinical data, 40 mg and 80 mg are effective doses with 80 mg providing added benefit for patients with more severe disease. Febuxostat also provides benefit in this patient population with comorbid conditions and has an advantage over allopurinol of not requiring dose adjustment in patients with mild to moderate renal impairment. Febuxostat doses of 40 mg and 80 mg are well tolerated and have a similar safety profile as the currently marketed allopurinol. The rates of CV events observed in the febuxostat clinical program were low. The potential CV risk was prospectively evaluated in the CONFIRMS Study and no difference in the rate of CV events was observed between febuxostat 80 mg and allopurinol; whereas, with its known risk of AHS, the risk in terms of severe rash is greater with allopurinol.

Febuxostat 40 mg and 80 mg doses are both recommended for approval to allow clinicians individualized dosing options. The 80 mg dose is more effective than 40 mg, especially in subjects with more severe disease as defined by the presence of tophi or higher sUA levels.

Overall, the benefits of febuxostat 40 mg and 80 mg clearly outweigh the risks and support approval of febuxostat for the treatment of hyperuricemia in patients with gout.

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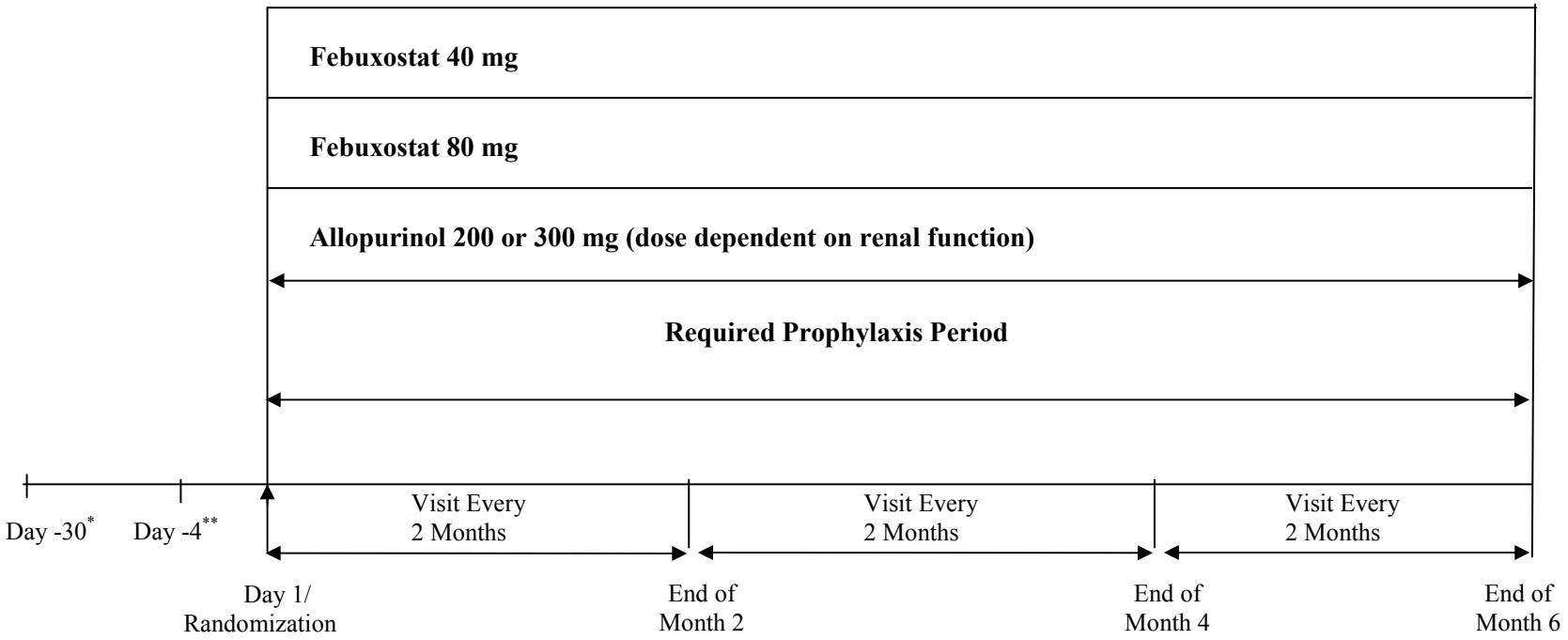
Appendix 1 Published Studies Reporting an Association between Hyperuricemia and Cardiovascular Risk

Study[a]	N	Ages (years); Subject Characteristics	Study Design	Duration	Results
Ioachimescu 2008	3098	18-87 yr; high risk of CV disease	Retrospective	7.5 yr	Each 1 mg/dL increase in sUA is associated with a 39% increase in incidence of cardiovascular death
Fang 2000	5926	25-76 yr; unspecified	Cross-sectional	16.4 yr	In men with sUA >7.1 mg/dL vs men with sUA <5.4 mg/dL, risk ratio for cardiovascular death was 1.77; in women with sUA > 5.6 mg/dL vs women with sUA <4.0 mg/dL risk ratio for death was 3.0
Bickel 2002	1,017	26-79 yr; unspecified	Prospective	2.2 yr	Subjects with mean sUA 8.2 mg vs those with mean sUA <4.6 mg/dl, has a 5-fold increase in mortality (17.1% vs 3.4%)
Strasek 2008	28,613	Mean 62 yr; women	Prospective	15.2 yr	Subjects with sUA ≥5.4 vs ≤3.7 had significant increase in CV mortality and fatal CHF
Strasek 2008	83,683	Mean 42 yr; men	Prospective	13.6 yr	Subjects with sUA ≥6.8 vs ≤4.6 had significant increase in CHF mortality and stroke
Madsen 2005	1595	Mean 65 yr; 78% male, all with at least 70% baseline coronary stenosis by angiography	Prospective	2.6 yr	170 died during study; sUA 6.4-13.8 mg/dL; sUA independent predictor for higher mortality
Bos 2006	4385	≥55 yr; no history of stroke	Prospective	8.4 yr	Increased sUA (>6.5 mg/dL) associated with increased incidence of MI

a See Reference List in this document for complete citations.

Appendix 2 Study Designs of the Phase 2 and 3 Studies

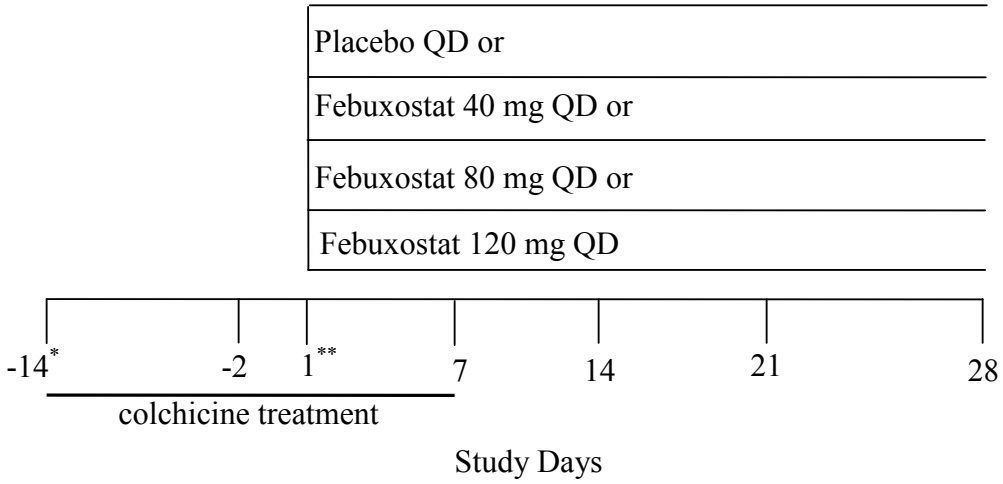
Figure 1 CONFIRMS Study Design



* Day -30 Screening Visit was required for subjects who were taking ULTs. These subjects received TAP-provided prophylaxis medications on the Day - 30 Screening Visit.

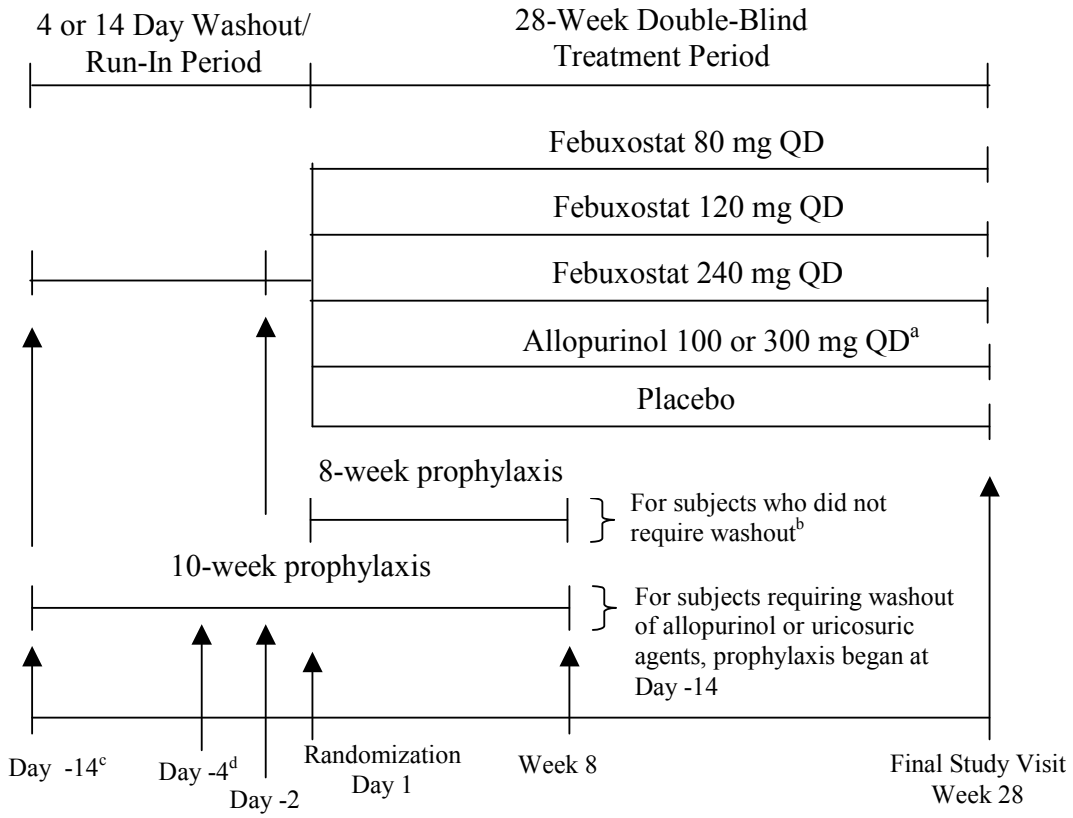
** Day -4 Visit was required for all subjects. It served as the Screening Visit for subjects who were not taking ULTs.

Figure 2 Dose-Ranging Study Design



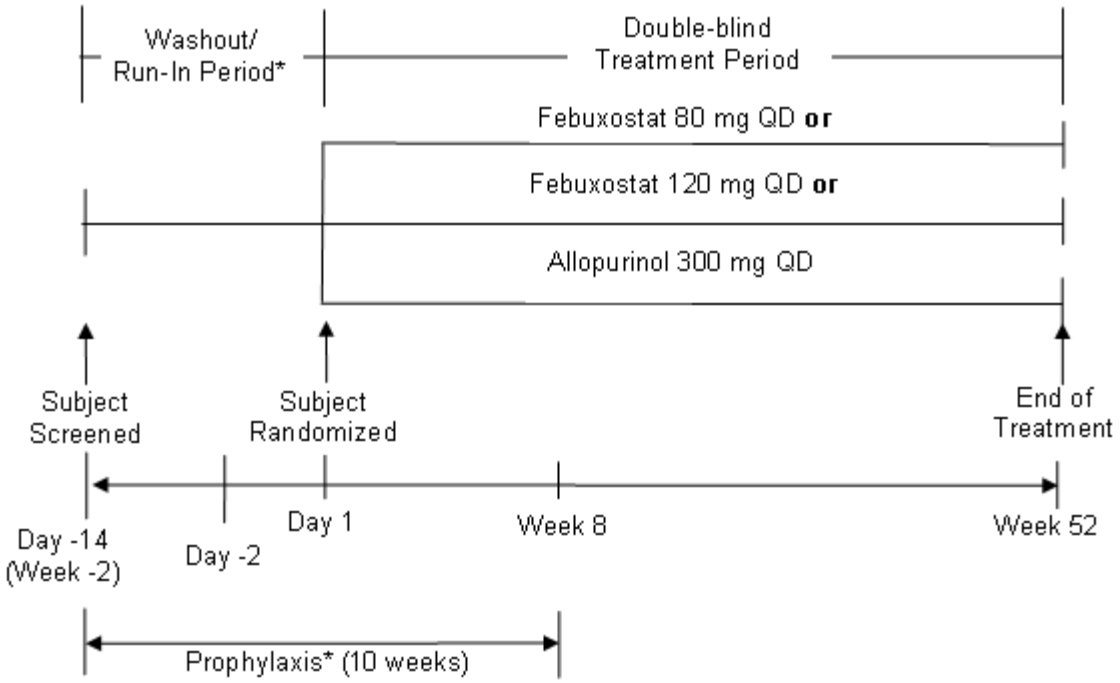
* Screening
** Randomization

Figure 3 APEX Study Design



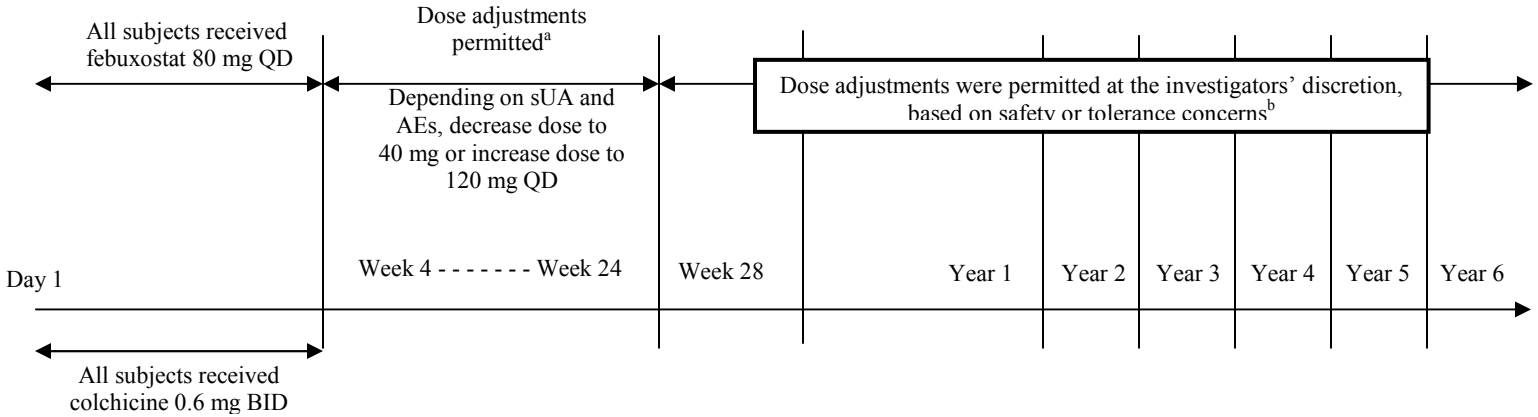
a Subjects randomly assigned to allopurinol who had serum creatinine ≤1.5 mg/dL at Day -2 received allopurinol 300 mg QD during the study; subjects randomly assigned to allopurinol who had serum creatinine >1.5 mg/dL and ≤2.0 mg/dL at Day -2 received allopurinol 100 mg QD.
b Subjects who were not receiving allopurinol or uricosuric agents prior to study began treatment with naproxen or colchicine at the Day 1 Visit.
c Screening Visit for subjects requiring washout of allopurinol or uricosurics.
d Screening Visit for subjects not requiring washout of allopurinol or uricosurics; all other subjects had a Day -4 Visit.

Figure 4 FACT Study Design



* Subjects who were not receiving allopurinol or uricosuric agents prior to the study began treatment with naproxen or colchicine at the Day 1 Visit. These subjects were not required to complete a 14-day Washout/Run-in Period prior to randomization; however, they were required to complete all Screening and Day -2 procedures. For subjects who did not require a Washout Period, the Screening Visit could have occurred anytime between Day -14 and Day -3.

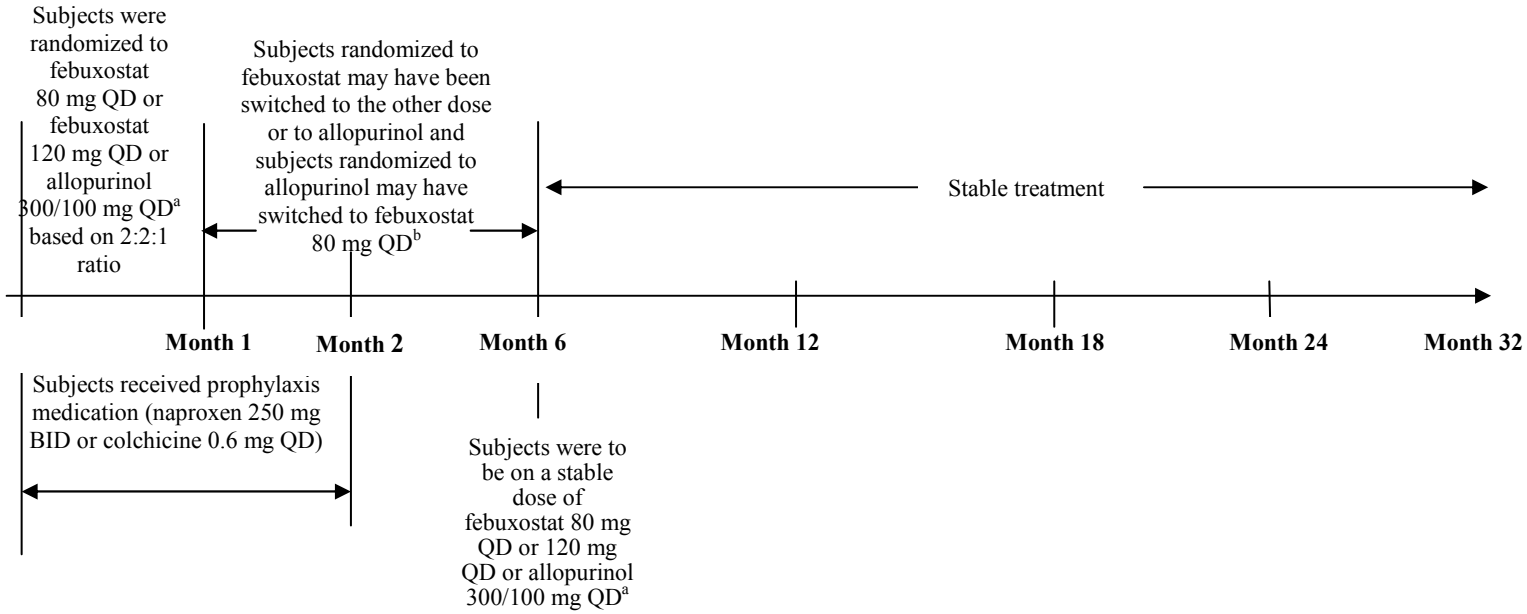
Figure 5 FOCUS Study Design



a Beginning with the Week 4 visit the investigator could decrease the dose to 40 mg QD or increase the dose to 120 mg QD. A maximum of 3 dose adjustments were allowed between Weeks 4 and 24 to achieve desired sUA levels. When sUA level remained >6.0 mg/dL, the dose could be increased to febuxostat 120 mg QD. When the sUA was <3.0 mg/dL, the dose could be reduced to 40 mg QD. Based on investigator assessment of adverse events and sUA.

b Subjects should have been on a stable dose from Week 24 to Week 28. Beginning Week 28, after reviewing adverse events and sUA levels, the investigator could make dose adjustments among febuxostat 40-mg, 80-mg, and 120-mg doses. TAP was notified of each dose adjustment and the reason for the adjustment.

Figure 6 EXCEL Study Design for Subjects Enrolled After Amendment Adding Allopurinol Treatment Group



a Allopurinol dose selected based on serum creatinine level

b Between Month 1 and Month 6, study drug may have been changed as follows:

- Subjects randomized to febuxostat may have had dose changed to 80 mg or 120 mg QD in order to maintain sUA ≥3.0 mg/dL and <6.0 mg/dL, due to an adverse event, or investigator's discretion.
- Subjects randomized to febuxostat 80 mg QD may have had study drug changed to allopurinol due to an adverse event or at investigator's discretion (after approval by TAP Medical Monitor).
- Subjects randomized to febuxostat 120 mg QD may have had study drug changed to allopurinol if sUA was >6.0 mg/dL, if an adverse event occurred, or at investigator's discretion (after approval by TAP Medical Monitor).
- Subjects randomized to allopurinol may have had study drug changed to febuxostat 80 mg QD if sUA was >6.0 mg/dL, if an adverse event occurred, or at investigator's discretion (after approval by TAP Medical Monitor). After a change to febuxostat, titration to 120 mg QD was allowed in order to maintain sUA ≥3.0 mg/dL and <6.0 mg/dL.

Appendix 3 Statistical Methodology for Phase 2 and 3 Controlled Studies

Statistical Methods for Primary Efficacy Endpoints

Efficacy analyses in the Phase 2 and 3 controlled studies were performed using a modified intent-to-treat (ITT) population, which was defined as all randomized subjects who took at least one dose of study drug and who had a baseline sUA level ≥ 8.0 mg/dL. Thirteen subjects (evenly distributed across 4 treatment groups) were excluded in the Dose-Ranging Study because their sUA samples were collected out of window; 10 subjects were excluded across the Phase 3 controlled studies for sUA levels <8.0 mg/dL just prior to randomization. Subjects receiving any dose of allopurinol (300, 200, or 100 mg) were analyzed together. All statistical tests and confidence intervals were 2-sided and all computations were performed prior to rounding unless otherwise specified.

Dose Ranging Study

The primary efficacy endpoint was the proportion of subjects whose serum urate level decreased to <6.0 mg/dL by Study Day 28. The last observation carried forward (LOCF) method was used to impute missing data for the primary efficacy endpoint with the baseline values carried forward, if necessary.

Each febuxostat dose group (40 mg, 80 mg, and 120 mg) was compared to the placebo group with Fisher's exact test. Superiority of a febuxostat dose group to the placebo group was declared if the p-value from Fisher's exact test was less than or equal to the critical significance level based on Hochberg's procedure.

Determination of Sample Size – Dose Ranging Study

One hundred twenty subjects (30 per treatment group) were planned to be enrolled in this study. This sample size provided at least 90% power to detect a difference between the febuxostat dose groups and placebo with a two-sided significance level of 0.05. The sample size calculation assumed a response rate of 80% for any of the febuxostat dose groups and 30% for placebo and allowed for a dropout rate of approximately 20%.

APEX Study

The primary efficacy endpoint was the proportion of subjects whose last three serum urate levels were <6.0 mg/dL. After applying the visit windows, each subject's last three serum urate levels, regardless of the subject's study completion status, were used to determine the subject's response for the primary efficacy endpoint. In order to be considered a responder, each of the last three serum urate levels must have been <6.0 mg/dL. If a subject prematurely discontinued from the study before at least three serum urate levels were obtained, the subject was considered a non-responder.

The objective of this study was to compare three doses of febuxostat (80 mg, 120 mg, and 240 mg) to placebo and allopurinol. The comparisons for the primary efficacy endpoint were

done sequentially using a closed testing procedure within each of three steps to ensure that the overall 0.05 level of significance was maintained.

The treatment groups were compared in the following sequential order:

1. Each febuxostat dose group was compared to the placebo group with a CMH test stratified by baseline renal function. Superiority of a febuxostat dose group to placebo was declared if the p-value from the CMH test was less than or equal to the critical significance level based on Hochberg's procedure. If each dose of febuxostat was shown to be superior to placebo, the procedure proceeded to step 2.
2. Binomial 97.5% confidence intervals, based on the normal approximation for the binomial distribution, were calculated for the differences in response rates between each dose group of febuxostat (80 mg and 120 mg) and the allopurinol treatment group. Non-inferiority to allopurinol was declared if the lower bound of the 97.5% confidence interval was greater than - 10%.
3. Each febuxostat dose group that was shown to be non-inferior to allopurinol in step 2 was compared to the allopurinol treatment group to test for superiority. The test for superiority was performed using a CMH test stratified by baseline renal function. If both dose groups of febuxostat were compared to allopurinol, superiority of a febuxostat dose group to the allopurinol treatment group was declared if the p-value from the CMH test was less than or equal to the critical significance level based on Hochberg's procedure and the response rate for the febuxostat dose group was higher than that for the allopurinol treatment group. If only one dose group of febuxostat was compared to allopurinol, superiority of the febuxostat dose group to the allopurinol treatment group was declared if the p-value from the CMH test was ≤0.05.

In the first step, Hochberg's method for multiple comparisons was used to ensure that the overall 0.05 level of significance was maintained for comparisons of the febuxostat 80 mg, 120 mg and 240 mg groups to placebo. In the second step, binomial 97.5% confidence intervals were used to adjust the overall 0.05 level of significance for comparisons of febuxostat 80 mg and 120 mg to allopurinol. In the third step, Hochberg's method for multiple comparisons was used to ensure that the overall 0.05 level of significance was maintained for comparisons of febuxostat 80 mg and 120 mg to allopurinol. Since the comparisons were done sequentially using a closed testing procedure within each step, adjustments to the overall alpha level were made only within each set of comparisons.

Additionally, comparisons were made between the febuxostat 240 mg and allopurinol group, between the allopurinol and placebo group, and between the febuxostat treatment groups using a CMH test stratified by baseline renal function. No adjustments to the alpha level were made for these comparisons.

Determination of Sample Size – APEX Study

A total of 1000 subjects (125 subjects in each of the placebo and febuxostat 240 mg treatment groups and 250 subjects in each of the febuxostat 80 mg, febuxostat 120 mg, and allopurinol treatment groups) were planned to be enrolled into this study. This sample size, based on the assumptions stated below, provided 1) at least 95% power to detect a difference of at least 45% between each of the febuxostat treatment groups and placebo for the primary efficacy endpoint; 2) at least 80% power to meet the non-inferiority criteria between at least one febuxostat treatment group and the allopurinol treatment group for the primary efficacy endpoint, and 3) at least 90% power to detect a 15% difference between a febuxostat treatment group and the allopurinol treatment group for the primary efficacy endpoint.

A larger number of subjects was required to show non-inferiority between the febuxostat 80 mg and 120 mg treatment groups and the allopurinol treatment group than was required to detect a difference between the placebo treatment group and the febuxostat treatment groups. Since the febuxostat 240 mg treatment group was included in this study to establish the safety profile of a high dose, comparisons between the febuxostat 240 mg treatment group and the allopurinol treatment group were not powered. Therefore, an unequal randomization was chosen for this study in which subjects were randomly assigned in a 1:2:2:1:2 ratio to receive placebo, febuxostat 80 mg, febuxostat 120 mg, febuxostat 240 mg, or allopurinol. For the determination of non-inferiority between each of the febuxostat treatment groups (80 mg and 120 mg) and the allopurinol treatment group, the sample size calculation assumed a true response rate of 60% for the allopurinol treatment group and at least 64% for the febuxostat dose groups, which was based on the results from the Dose-Ranging study and a literature review of historical allopurinol data.

FACT Study

The primary efficacy endpoint was the proportion of subjects whose last three serum urate levels were <6.0 mg/dL. After applying the visit windows, each subject's last three serum urate levels, regardless of the subject's study completion status, were used to determine the subject's response for the primary efficacy endpoint. In order to be considered a responder, each of the last three serum urate levels must have been <6.0 mg/dL. If a subject prematurely discontinued from the study before at least three serum urate levels were obtained, the subject was considered a non-responder.

The objective of this study was to compare different oral doses of febuxostat (80 mg and 120 mg) to allopurinol. The comparisons for the primary efficacy endpoint were done sequentially using a closed testing procedure within each of two steps to ensure that the overall 0.05 level of significance was maintained.

The treatment groups were compared in the following sequential order:

1. Binomial 97.5% confidence intervals, based on the normal approximation for the binomial distribution, were calculated for the differences in response rates between each dose group of febuxostat (80 mg and 120 mg) and the allopurinol treatment

group. Non-inferiority to allopurinol was declared if the lower bound of the 97.5% confidence interval was greater than -10%.

2. Each febuxostat dose group that was shown to be non-inferior to allopurinol in step 1 was compared to the allopurinol treatment group to test for superiority. The test for superiority was performed using Fisher's exact test. If both dose groups of febuxostat were compared to allopurinol, superiority of a febuxostat dose group to the allopurinol treatment group was declared if the p-value from Fisher's exact test was less than or equal to the critical significance level based on Hochberg's procedure and the response rate for the febuxostat dose group was higher than that for the allopurinol treatment group. If only one dose group of febuxostat was compared to allopurinol, superiority of the febuxostat dose group to the allopurinol treatment group was declared if the p-value from Fisher's exact test was ≤0.05.

In the first step, binomial 97.5% confidence intervals were used to adjust the overall 0.05 level of significance for both comparisons of febuxostat to allopurinol. In the second step, Hochberg's method for multiple comparisons was used to ensure that the overall 0.05 level of significance was maintained for comparisons of each febuxostat treatment group to allopurinol. If only one dose group of febuxostat was tested for superiority to allopurinol in the second step, a level of significance of 0.05 was used. Since the comparisons were done sequentially using a closed testing procedure within each step, adjustments to the overall alpha level were made only within each set of comparisons.

An additional comparison was made between the febuxostat 80 mg and 120 mg treatment groups with no adjustment to the alpha level.

Determination of Sample Size – FACT Study

A total of 750 subjects (250 per treatment group) were planned to be enrolled into this study. The sample size provided 1) at least 80% power to meet the non-inferiority criteria between at least one febuxostat treatment group and the allopurinol treatment group for the primary efficacy endpoint based on the assumptions below and 2) at least 90% power to detect a 15% difference between a febuxostat treatment group and the allopurinol treatment group for the primary efficacy endpoint.

For the determination of non-inferiority between the febuxostat treatment groups and the allopurinol treatment group, the sample size calculation assumed a true response rate of 60% for the allopurinol treatment group and at least 64% for the febuxostat dose groups, which was based on the results from the Dose-Ranging study and a literature review of historical allopurinol data.

CONFIRMS Study

The primary efficacy endpoint was the proportion of subjects whose final serum urate level was <6.0 mg/dL. All serum urate levels collected from the start of the study to within 1 day, inclusive, of a subject's final dose were included in the primary efficacy analyses. If a subject prematurely discontinued from the study, then the subject's latest visit with a serum urate level

occurring no later than 1 day postdosing was used for the Final Visit. A subject's baseline value was used in the analysis if no post baseline serum urate level was obtained.

The objective of this study was to compare febuxostat 40 mg and febuxostat 80 mg doses to allopurinol. The primary comparison was febuxostat 40 mg versus allopurinol. Secondary comparisons of febuxostat 80 mg versus allopurinol and of febuxostat 40 mg versus febuxostat 80 mg were also performed.

For the primary comparison of febuxostat 40 mg versus allopurinol, the treatment groups were compared in the following sequential order.

1. In the first step, the 40 mg febuxostat treatment group was compared to the allopurinol treatment group to test for non-inferiority. Binomial 95% confidence intervals, based on the normal approximation for the binomial distribution, were calculated for the difference between the febuxostat 40 mg and the allopurinol treatment groups. Non-inferiority to allopurinol was declared if the value of the lower bound of the 95% confidence interval for the difference (ie, febuxostat 40 mg - allopurinol) was greater than -10%.
2. If febuxostat 40 mg was shown to be non-inferior to allopurinol in step 1, then a test for superiority to allopurinol was performed using Fisher's exact test. Superiority of febuxostat 40 mg to allopurinol was declared if the p-value from Fisher's exact test was ≤ 0.05.

Because of the closed testing procedure, no adjustments to the overall significance level were made. Secondary treatment comparisons were made comparing febuxostat 80 mg to allopurinol, and febuxostat 40 mg to febuxostat 80 mg using Fisher's exact test with two-tailed 0.05 significance level.

Determination of Sample Size – CONFIRMS Study

A total of 2250 subjects (750 per treatment group) were planned to be enrolled into this study. The sample size provided 1) at least 90% power to meet the non-inferiority criteria between febuxostat 40 mg and allopurinol for the primary efficacy endpoint; 2) at least 90% power to detect a 10% difference between febuxostat 40 mg and allopurinol, for the primary efficacy endpoint; and 3) at least 90% power to detect a 10% difference for the secondary treatment comparison between febuxostat 40 mg and 80 mg for the primary efficacy endpoint.

For the determination of non-inferiority between the febuxostat 40 mg treatment group and the allopurinol treatment group, the sample size calculation assumed a true response rate of 50% for both the allopurinol and febuxostat 40 mg treatment groups. The response rate estimate of 50% was based on the Final Visit response rates observed for febuxostat 40 mg in the Dose-Ranging study and for allopurinol in the APEX and FACT studies.

Assuming an adjudicated APTC event rate of 0.6% for both febuxostat treatment groups and the allopurinol group, the sample size of 750 per treatment group provided a 90% and 80% probability to expect that the observed relative risk of either febuxostat group to allopurinol was

no greater than 2.344 and 1.750, respectively. The APTC event rate estimate of 0.6% is representative of the event rate observed in the APEX and FACT studies for all febuxostat doses combined.

Multivariate Regression Analyses

The effects of treatment group, baseline serum urate level, average postbaseline serum urate level, average postbaseline percent change in serum urate level, and baseline palpable tophus presence on the proportion of subjects requiring treatment for a gout flare between Week 24 and Week 28 or between Week 48 and Week 52 were further explored via a multivariate logistic regression model. Baseline serum urate level, average postbaseline serum urate level, and average postbaseline percent change in serum urate level were treated as continuous data in the models.