Briefing Document for the Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee
11 January 2019

Uloric (febuxostat)

NDA 021856

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Advisory Committee Briefing Materials: Available for Public Release

1.0 EXECUTIVE SUMMARY

Febuxostat is a potent, nonpurine, selective xanthine oxidase inhibitor (XOI). It was approved on 13 February 2009 in the United States (US) at doses of 40 and 80 mg once daily (QD) for the chronic management of hyperuricemia in patients with gout. It is not recommended for treatment of asymptomatic hyperuricemia in the US. It was initially approved in the European Union (EU) (international birth date [IBD] 21 April 2008), and febuxostat has since been approved in 85 countries worldwide. In some ex-US countries, febuxostat is also indicated for the treatment of hyperuricemia in patients without gout and/or prevention and treatment of hyperuricemia in adult patients undergoing chemotherapy for hematologic malignancies at intermediate-to-high risk of tumor lysis syndrome. Approved doses vary in different regions and range from 10 to 120 mg. The estimated global exposure is 15.1 million person-years (PY); the total estimated US exposure is 1.4 million PY.

Gout has an estimated prevalence of 8 to 9 million adults in the US [1]. Gout is 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 (CV) disease, chronic kidney disease (CKD), and metabolic syndrome [2-4]. The most frequent initial clinical manifestation of gout is a flare of inflammatory arthritis, which develops over a few hours, usually involves a single lower extremity (LE) joint, and is severely disabling due to extreme pain, swelling, and loss of joint function. In most patients, the initial attack resolves spontaneously and completely within a week or 2, but in most instances, recurs intermittently and progressively more often. The underlying metabolic aberration in gout is hyperuricemia. It is defined as an elevation in plasma or serum uric acid (sUA) ≥6.8 mg/dL, the limit of urate solubility, which signals a risk for gout through crystal formation and deposition. Over time, the crystal deposition and inflammation can result in progressive joint damage and erosion, with the formation of masses of urate crystals in a chronic inflammatory background (called tophi) that can be deforming and disabling. Patients who experience frequent gout flares or have tophi present have a lower quality of life [5]. Adequate control of gout not only reduces the physical manifestations of the disease, it also reduces associated healthcare burdens.

Treatment and prevention of gout traditionally involved anti-inflammatory medication for acute attacks (eg, colchicine, corticosteroids or nonsteroidal anti-inflammatory drugs [NSAIDs]), and urate-lowering therapy (ULT) for long-term management of hyperuricemia and prevention of urate crystal-induced damage. To achieve the optimum treatment goals for gout, the American College of Rheumatology (ACR) gout guidelines recommends that a ULT include a target serum urate goal of <6.0 mg/dL for most gout patients, with a goal of <5.0 mg/dL in patients with tophaceous disease or more severe gout [6].

Overall, there are few ULTs available and each agent has limitations. ULTs can be grouped into 3 categories based on their mechanism of action:

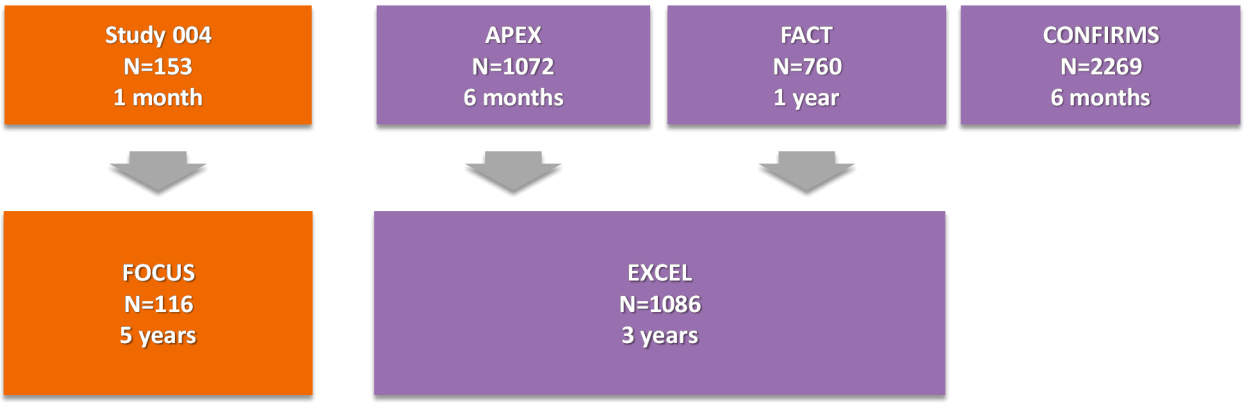
- XOIs: reduce uric acid production (febuxostat, allopurinol).
- Uricosurics: promote urinary uric acid clearance (probenecid, lesinurad).

- Recombinant uricase: a biological agent that enzymatically degrades circulating uric acid (pegloticase).

XOIs are the consensus first-line ULT, a role most often fulfilled with allopurinol, or alternatively febuxostat [6].

The clinical development program for febuxostat supporting approval is shown in Figure 1.a.

Figure 1.a Febuxostat Clinical Development Program Supporting Approval



Study 004 (phase 2), APEX, FACT, and CONFIRMS (phase 3) were randomized, double-blind studies. FOCUS and EXCEL were open-label extension studies.

Both febuxostat 40 mg and 80 mg doses demonstrated efficacy in urate lowering in subjects with gout. Febuxostat demonstrated the ability to achieve sUA targets of <6.0 and/or <5.0 mg/dL better than commonly prescribed doses (≤300 mg/day) of allopurinol in current clinical practice, including in subjects with sUA levels ≥10 mg/dL or who have tophi. Additionally, febuxostat decreases acute flares and reduces tophus size over time through persistent long-term urate-lowering effects. More importantly, unlike allopurinol, febuxostat has been approved without dose adjustment for patients with gout and mild-to-moderate renal impairment (estimated creatinine clearance [eCrCl] of 30 to 90 mL/min), and febuxostat 40 mg is also approved in patients with severe renal impairment (eCrCl of <30 mL/min).

In the initial 2 phase 3 studies (APEX and FACT), Antiplatelet Trialists' Collaborative (APTC) events (CV death, nonfatal myocardial infarction [MI], nonfatal stroke) were numerically low, but there was an imbalance in the rate of events for febuxostat 80 and 120 mg compared with allopurinol or placebo (Table 5.b). As a result, Takeda conducted an additional phase 3 study (CONFIRMS) that assessed safety and efficacy of the febuxostat 40 and 80 mg doses compared with allopurinol in subjects with hyperuricemia and gout. CONFIRMS did not show a higher rate of CV thromboembolic events with febuxostat than with allopurinol (Table 5.c). A pooled analysis of the randomized phase 3 studies revealed a numerical imbalance in the number of CV thromboembolic events in the composite of CV deaths, nonfatal MI, and nonfatal strokes in subjects treated with febuxostat compared with allopurinol as summarized in Table 1.a.

Table 1.a Adjudicated Major CV Events From Pooled Analysis of Phase 3 Randomized Controlled Studies (APEX, FACT, CONFIRMS)

	Events, n (rate per 100 subject years) 95% CI	
	Febuxostat N = 2690	**Allopurinol N = 1277**
All APTC events	10 (0.74) 0.36, 1.37	4 (0.60) 0.16, 1.53
CV death	3 (0.22) 0.05, 0.65	2 (0.30) 0.04, 1.08
Nonfatal MI	5 (0.37) 0.12, 0.87	2 (0.30) 0.04, 1.08
Nonfatal stroke	2 (0.15) 0.02, 0.54	0 0.00, 0.55

APTC: Antiplatelet Trialists' Collaborative; CV: cardiovascular; MI: myocardial infarction.
Adjudication was done prospectively in CONFIRMS and retrospectively in APEX and FACT.

These data were reviewed by the Food and Drug Administration (FDA) Arthritis Advisory Committee in November 2008, where based on the evidence presented the committee voted 12 to 0 recommending approval with 1 abstention. The committee highlighted that there was adequate evidence of the efficacy and safety of febuxostat. However, the advisory committee agreed that the CV safety risk had not been fully elucidated and a postapproval study should be conducted to further assess the CV safety of the drug.

Febuxostat was approved with a Warnings and Precautions for Cardiovascular Events in the prescribing information highlighting the rate of CV events from the pooled analysis and a postmarketing requirement to conduct a randomized controlled study of adequate size and duration to determine whether febuxostat was associated with an increase in the risk of serious adverse CV outcomes as compared with allopurinol [7].

The CARES study was conducted to fulfill this requirement, and was designed to assess if febuxostat was noninferior to allopurinol for the primary endpoint of the major adverse cardiac event (MACE) composite (CV death, nonfatal MI, nonfatal stroke, and unstable angina with urgent coronary revascularization) in subjects with gout and a high CV risk profile [8]. The study had a prespecified noninferiority margin of 1.3 for the hazard ratio (HR) for the primary endpoint. The study protocol was finalized following discussions and agreement with FDA. The study was initiated in 2010 and completed in 2017.

Subjects with major concurrent CV disease were randomly assigned to receive febuxostat or allopurinol and stratified by kidney function. Doses were titrated to achieve target sUA <6 mg/dL. Unlike febuxostat, doses of allopurinol were titrated based on kidney function. A total of 6190 subjects were randomized into the study and were followed for a median of 32 months. The cumulative duration of study participation was similar between treatment groups. Baseline and demographic characteristics were similar between treatment groups, and most subjects were

male and white; the overall mean age was 64.8 years. Over half in each treatment group had moderate renal impairment (eCrCl 30 to 59 mL/min).

The CARES study results are shown in Table 1.b.

- For the primary endpoint of MACE composite, CARES showed that febuxostat was noninferior to allopurinol.
- When analyzing the individual components of MACE as secondary endpoints, the rate of CV death was higher with febuxostat compared with allopurinol whereas the individual rates for nonfatal MI, nonfatal stroke, and urgent revascularization for unstable angina did not differ between febuxostat and allopurinol. All-cause mortality was also higher with febuxostat than allopurinol due to the higher rate of CV deaths [9].

Table 1.b Analysis of MACE and Each Event in the MACE Composite (mITT)

	Febuxostat N = 3098	Allopurinol N = 3092	Hazard ratio (95% CI) [a]
Composite primary endpoint	335 (10.8)	321 (10.4)	1.03 (0.87, 1.23) [b]
CV death	134 (4.3)	100 (3.2)	1.34 (1.03, 1.73)
Nonfatal MI	111 (3.6)	118 (3.8)	0.93 (0.72, 1.21)
Nonfatal stroke	71 (2.3)	70 (2.3)	1.01 (0.73, 1.41)
Unstable angina with urgent coronary revascularization	49 (1.6)	56 (1.8)	0.86 (0.59, 1.26)

Source: White et al [9].
CV: cardiovascular; MACE: major adverse cardiac event; MI: myocardial infarction; mITT: modified intent-to-treat.
Analysis based on mITT.
[a] Febuxostat to allopurinol.
[b] 95% adjusted CI.

- Because of the higher rate of CV death, multiple potential risk factors were evaluated including: subject baseline characteristics, changes in electrolytes, changes in blood pressure or heart rate, and gout flare rates. Overall, there was no biologically plausible explanation for the higher rate of CV death.
- The design of the CARES study has both strengths and limitations:
  - CARES was the first cardiovascular outcomes trial (CVOT) of urate lowering drugs in subjects with gout and major CV or cerebrovascular disease. It was the largest, long-term, double-blind, randomized study that incorporated a predefined, comprehensive adjudication process for major CV endpoints to address the question of CV risk of febuxostat compared with allopurinol. Moreover, the study allowed for direct comparison of allopurinol and febuxostat using a treat-to-target dose-titration scheme.
  - The CARES study is limited by the lack of a placebo arm, which precludes determination of either study drugs' impact in CV risk compared with an untreated gout population. Additionally, because many subjects enrolled had previous exposure to allopurinol, this

may create a potential bias for underestimation of adverse events with allopurinol, as subjects who previously did not tolerate allopurinol would not have enrolled. The CARES study was not designed for noninferiority for the individual MACE component endpoints. Furthermore, type 1 error control and noninferiority assessment were done solely for the primary endpoint and not the individual MACE components.

- In this study, there were many subjects who discontinued from study drug and many subjects who did not complete follow-up. High rates of discontinuation of treatment can lead to concerns of missing a significant difference between treatment groups in the primary or secondary outcomes. Analyses were conducted to assess the potential impact of missing data including overall dropout rates, reason for dropout, timing of dropout, baseline characteristics of subjects who dropped out, and multiple imputation. These additional analyses were consistent with the modified intent-to-treat (mITT) analyses.

- There was no signal for increased CV risk for febuxostat from nonclinical data or a thorough corrected QT interval (QTc) study conducted in healthy subjects. Postmarketing signal detection also revealed no signal for CV events or CV death with febuxostat. Published studies in the literature have varied results and do not support an increased CV risk with febuxostat.

Further understanding of the CV profile for febuxostat and allopurinol may be gained from an on-going CV safety study being conducted in Europe as a postauthorization requirement by Menarini (a partner of Teijin Pharmaceutical Companies, Takeda's alliance partner) the Febuxostat versus Allopurinol Streamlined Trial (FAST) [10]. It is a prospective, randomized, parallel group, open-label, blinded endpoint (PROBE) study comparing febuxostat with allopurinol conducted in the clinical setting (general practitioners and specialist). It is designed as a noninferiority study and the primary endpoint is first occurrence of the APTC CV endpoint of nonfatal MI, nonfatal stroke, or CV death. The recruitment in FAST ended in January 2018 and the clinical study report is expected by August 2020.

Following comprehensive clinical assessments and exploratory analyses, Takeda has been unable to determine any contributing factors or a population at risk for the higher rate of CV death observed in the CARES study. Accounting for the totality of the evidence, including the lack of concordance between the individual MACE components, the inability to explain the finding and the absence of biological plausibility, there remains uncertainty about the reliability of the observation.

The seriousness of the observation in CARES makes it important that physicians are informed so they can consider the benefits and risks of febuxostat compared with other treatment options for each individual patient based upon the best available information. The CARES data has been widely disseminated to the medical community over the past several months including publication of CARES in the *New England Journal of Medicine* in March 2018 [9]. Takeda will continue to share the CARES study findings with the medical community.

In addition, Takeda proposes to update the prescribing information with the CARES study data to include CV death in the Warnings and Precautions section and describe the CARES study

results in the clinical trials section and all other relevant sections. Specific labeling language will be discussed with FDA during labeling review. Takeda will communicate these important updates following label approval, via distribution of a Dear Healthcare Provider (HCP) letter to HCPs, pharmacies, and professional societies.

Febuxostat continues to be an important treatment option in the management of hyperuricemia in patients with gout. Considering the seriousness of the disease, the limited treatment options, the clinical use of febuxostat over 10 years and its safety profile, including the totality of the CV safety data, the benefit-risk assessment for febuxostat remains positive.

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ACR	American College of Rheumatology
AHS	allopurinol hypersensitivity syndrome
ALT	alanine aminotransferase
APTC	Antiplatelet Trialists' Collaborative
AST	aspartate aminotransferase
CEC	Cardivascular Endpoint Committee
CHD	coronary heart disease
CHF	congestive heart failure
CKD	chronic kidney disease
CPH	Cox proportional hazard
CV	cardiovascular
CVD	cardiovascular disease
CVOT	cardiovascular outcomes trial
DDI	drug-drug interaction
DMC	Data Monitoring Committee
ECG	electrocardiogram
EU	European Union
eCrCl	estimated creatinine clearance
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
HCP	healthcare provider
HR	hazard ratio
IBD	International Birth Date
IBW	ideal body weight
IV	intravenous
LE	lower extremity
MACE	major adverse cardiac event
MAH	Marketing Authorisation Holder
MI	myocardial infarction
mITT	modified intent-to-treat
MRI	magnetic resonance imaging
NHANES	National Health and Nutrition Examination Survey
NSAID	nonsteroidal anti-inflammatory drug
PMS	postmarketing studies
PPI	proton pump inhibitor
PROBE	prospective, randomized, parallel group, open-label, blinded endpoint
PT	preferred term
PY	patient-years, person-years
QD	once daily

QTc	corrected QT interval
QTcB	QT interval with Bazett correction method
QTcF	QT interval with Fridericia correction method
RR	relative risk
SAP	statistical analysis plan
SMQ	standardized MedDRA query
sUA	serum uric acid
TIA	transient ischemic attack
TEAE	treatment-emergent adverse event
UK	United Kingdom
ULN	upper limit of normal
ULT	urate-lowering therapy
US	United States
XOI	xanthine oxidase inhibitor

Studies Referenced in the Document

Alias (Study Number)	Full Study Title
APEX (C02-009)	Allopurinol and Placebo Evaluation of Febuxostat
CARES (TMX-67-301)	Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities
CONFIRMS (F-GT06-153)	Confirmation of Febuxostat in Reducing and Maintaining Serum Urate
EXCEL (C02-021)	Febuxostat /Allopurinol Comparative Extension Long-Term Study
FACT (C02-010)	Febuxostat versus Allopurinol Controlled Trial
FAST	Febuxostat versus Allopurinol Streamlined Trial
FOCUS (TMX-01-005)	Febuxostat Open Label of Urate-Lowering Efficacy and Safety
FREED	Febuxostat for Cerebral and CaRdiorenovascular Events PrEvEntion StuDy
MRFIT	Multiple Risk Factor Intervention Trial

2.0 BACKGROUND AND REGULATORY HISTORY

Febuxostat is a potent, nonpurine, selective XOI. Takeda is the marketing authorization holder (MAH) for febuxostat in the US, Canada, and Mexico; Takeda's alliance partner Teijin or its partners are MAH in the rest of the world. Febuxostat was approved in February 2009 in the US for the chronic management of hyperuricemia in patients with gout. In the US, the recommended starting dose is 40 mg QD; 80 mg is recommended for patients who do not achieve an sUA <6 mg/dL after 2 weeks with 40 mg. Febuxostat is not recommended for treatment of asymptomatic hyperuricemia in the US. It was initially approved in the EU (IBD of 21 April 2008), and febuxostat has since been approved in 85 countries worldwide. Further, in some ex-US countries, febuxostat is also indicated for treatment of hyperuricemia in patients without gout and/or prevention and treatment of hyperuricemia in adult patients undergoing chemotherapy for hematologic malignancies at intermediate to high risk of tumor lysis syndrome. Approved doses vary in different regions and range from 10 to 120 mg. The estimated global exposure is 15.1 million PY; the total estimated US exposure is 1.4 million PY.

During review of the initial 2 phase 3 studies (APEX and FACT), FDA determined that there was an imbalance in CV events in subjects receiving febuxostat (Table 5.b). In APEX and FACT, APTC events were numerically low, but there was an imbalance in the rate of events for febuxostat 80 and 120 mg. Because of the small number of events in each study arm and the limited exposure on allopurinol in the long-term extension studies, there was uncertainty whether the findings represented an increased risk of CV events with febuxostat. Because of this uncertainty, FDA required Takeda to provide further data to clarify the CV risks of the proposed doses and/or provide data on the safety and efficacy of lower doses of febuxostat.

As a result, Takeda conducted an additional phase 3 study (CONFIRMS) that assessed safety and efficacy of the febuxostat 40 and 80 mg doses compared with allopurinol in 2269 subjects with hyperuricemia and gout. To address the potential problems involved with post hoc adjudication in the previous studies, this study included a cardiovascular endpoint committee (CEC), who performed adjudication of all deaths and CV adverse events. APTC events were prespecified and included CV death, nonfatal MI, and nonfatal stroke. As shown in Table 5.c, examination of CV events in CONFIRMS did not show a higher rate of CV thromboembolic events with febuxostat than with allopurinol control. The overall mortality rate and CV mortality rate were not increased. This study did not confirm the previous observation of a higher rate of CV events with febuxostat than with allopurinol.

A pooled analysis of the 3 phase 3 randomized controlled studies (APEX, FACT, and CONFIRMS) revealed a numerical imbalance in the number of CV thromboembolic events in the composite of CV deaths, nonfatal MI, and nonfatal strokes in subjects treated with febuxostat compared with allopurinol, as shown in Table 2.a.

Table 2.a Adjudicated Major CV Events From Pooled Analysis of Phase 3 Randomized Controlled Studies (APEX, FACT, CONFIRMS)

	Events, n (rate per 100 subject years) 95% CI	
	Febuxostat N = 2690	**Allopurinol N = 1277**
All APTC events	10 (0.74) 0.36, 1.37	4 (0.60) 0.16, 1.53
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APTC: Antiplatelet Trialists' Collaborative; CV: cardiovascular; MI: myocardial infarction.
Adjudication was done prospectively in CONFIRMS and retrospectively in APEX and FACT.

These data were reviewed by the FDA Arthritis Advisory Committee in November 2008, where on the basis of the evidence presented, the committee voted 12 to 0 recommending approval with 1 abstention. The committee highlighted the adequate evidence of the efficacy and safety of febuxostat. However, they agreed that the CV safety risk had not been fully elucidated and a postapproval study should be conducted to further assess the CV safety.

Febuxostat was approved with a Warnings and Precautions on Cardiovascular Events in the prescribing information. FDA also required Takeda to conduct a postmarketing, randomized, controlled study of adequate size and duration to determine whether febuxostat was associated with an increase in the risk of serious adverse CV outcomes as compared with allopurinol. The CARES study was conducted to assess whether febuxostat was noninferior to allopurinol in its effect on major CV events in hyperuricemic subjects with gout who had a high CV risk profile. A summary of the key regulatory interactions regarding the CVOT (Postmarketing Requirement 811-1) is presented in Table 2.b.

Table 2.b Key US-FDA Interactions Related to the CVOT

Date	Description of Key FDA Submissions/Communications Related to the CVOT
20 Jan 2010	FDA agreement on the study protocol.
19 Oct 2017	Takeda informed the FDA on study completion, topline study results, and next steps.
02 Nov 2017	Takeda received a notification that FDA had opened a Tracked Safety Notification for Uloric regarding an increased risk of CV death from the CVOT.
15 Nov 2017	FDA issued a DSC to inform the public that: • Preliminary results from a safety clinical study show an increased risk of heart-related death with febuxostat (Uloric) compared with allopurinol. • FDA will conduct a comprehensive review and will update the public with any new information.
19 Jan 2018	Supplemental NDA 21856/S-013 filed to provide the CARES clinical study report and update the US Prescribing Information based on the results of the CVOT.
22 Aug 2018	FDA updated the DSC dated 15 Nov 2017 to inform the public that: • FDA had received the results of the CARES study and are conducting a comprehensive review. • FDA will also convene an advisory committee meeting of external experts in early 2019 to discuss these study results and the results of FDA review.
30 Nov 2018	FDA published a notice in the Federal Register that FDA will convene a joint meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee to review the CARES study results, benefit-risk assessment and potential regulatory actions.

CARES: Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities; CV: cardiovascular; CVOT: cardiovascular outcomes trial; DSC: Drug Safety Communication; FDA: Food and Drug Administration; NDA: New Drug Application; US: United States.

3.0 GOUT OVERVIEW

3.1 Gout Disease Background

Gout is the most common form of inflammatory arthritis [11,12] with an estimated prevalence of 8 to 9 million adults in the US, based on survey data from the National Health and Nutrition Examination Survey (NHANES) 2007 to 2008 [1]. Gout incidence has increased in the US approximately 30% to 40% over the past 3 decades, likely reflecting demographic factors such as longevity and obesity. The condition affects primarily middle-aged and older men and postmenopausal women, and prevalence increases with age.

Gout is a serious health condition characterized by flares of acute arthritis, chronic gouty arthropathy, tophi development, and uric acid urolithiasis. The most frequent initial clinical manifestation of gout is a flare of inflammatory arthritis, which develops over a few hours, usually involves a single LE joint, and is severely disabling due to extreme pain, swelling, and loss of joint function. In most, the initial attack-resolves spontaneously and completely within a week or 2, but in most instances, recurs intermittently and more often.

Gout results from an inflammatory response to urate crystals deposited in connective tissues from extracellular fluid saturated with urate. This biochemical abnormality is reflected in the blood and is referred to as hyperuricemia. Hyperuricemia is defined as serum or plasma sUA >6.8 mg/dL, the limit of urate solubility, which signals a risk for gout through crystal formation and deposition. Uric acid is the end-product of purine metabolism in humans. Uric acid production and disposal are normally balanced processes in which about two-thirds of daily uric acid elimination are by urinary excretion and about one-third by the excretion into the gastrointestinal tract. Impaired renal or gastrointestinal uric acid clearance is the primary basis of hyperuricemia in about 90% of patients with gout; the remaining 10% of patients with gout have increased uric acid production.

Over time, the crystal deposition and inflammation can result in progressive joint damage and erosion, with the formation of urate crystals masses in a chronic inflammatory background (called tophi), which can be deforming and disabling. Patients who experience frequent gout flares or have tophi present have a lower quality of life [5].

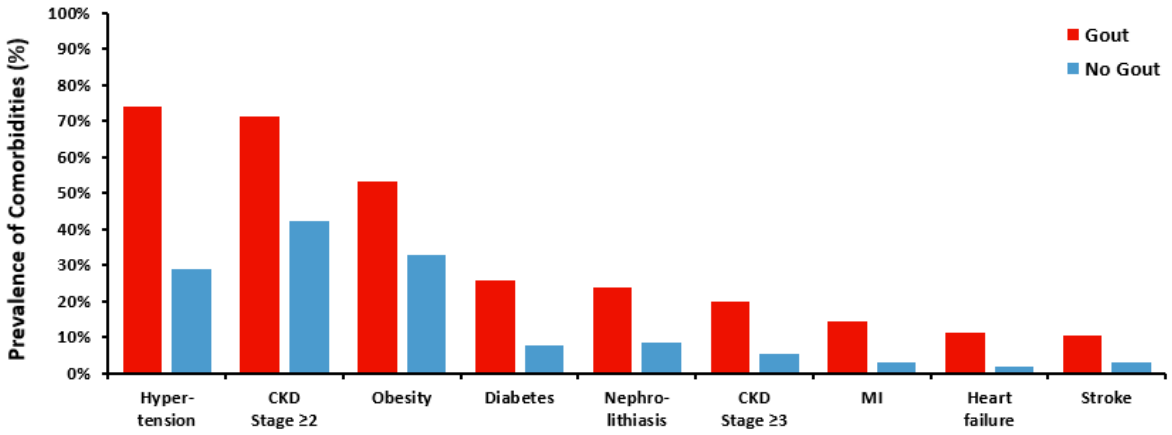
Adequate control of gout not only reduces the physical manifestations of the disease, it also reduces associated healthcare burdens. In several published studies, increases in healthcare utilization and costs, as measured by frequent primary care visits, ambulatory visits, emergency room visits, and hospital admissions, was higher in patients with the presence of untreated or inadequately controlled gout and gout flares [13-15].

3.2 Cardiorenal Comorbidities

Patients with gout are not only at risk in developing disabling and deforming physical manifestations, they also have higher risk for serious comorbid conditions such as CV, renal, and metabolic disorders that are associated with hyperuricemia, gout, or both. The difference in prevalence of these comorbidities between patients with or without gout was demonstrated in NHANES 2007 to 2008 [16]. The associations are most common with hypertension, CKD ≥2 (ie,

estimated glomerular filtration rate [eGFR] ≤90 mL/min/1.73 m²), obesity, diabetes, and CV disease as shown Figure 3.a.

Figure 3.a Serious Comorbidities Associated With Gout: NHANES 2007-2008



CKD: chronic kidney disease; MI: myocardial infarction; NHANES: National Health and Nutrition Examination Survey.

The most serious associations of gout are those with CV disease, CV death, and all cause death. It has been shown that patients with gout have higher risk for these than patients without gout. In a large observational cohort study of male health professionals followed for 12 years [17], the rates of all-cause mortality, CV death, and fatal coronary heart disease (CHD) were increased among patients with gout relative to those of patients without gout. Additionally, in the Multiple Risk Factor Intervention Trial (MRFIT), Krishnan et al also found higher rates of CV events in patients with gout compared with patients without gout (Table 3.a) [11,18].

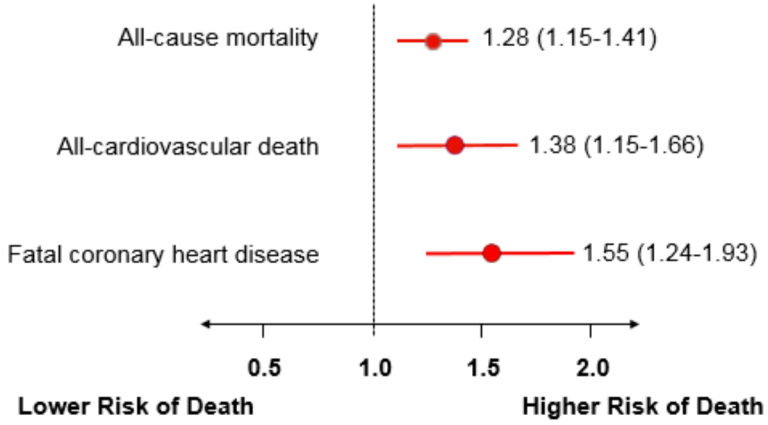
Table 3.a Rates (PY) of Nonfatal MI, CV Death, and All Cause Deaths in Gout and No Gout

	Health Professionals Follow-up Study [a]		MRFIT Study [b,c]	
PY	513,728		~83,629 [b]/~15,255 [c]	
	Gout	**No Gout**	**Gout**	**No Gout**
Nonfatal MI	0.46	0.24	0.43 [b]	0.34 [b]
CV deaths	0.40	0.16	1.03 [c]	0.80 [c]
All cause deaths	1.46	0.70	2.09 [c]	1.8 [c]

CV: cardiovascular; MI: myocardial infarction; MRFIT: Multiple Risk Factor Intervention Trial; PY: person-years.
[a] Choi et al [17].
[b] Krishnan et al [18].
[c] Krishnan et al [11].

The relative risks (RRs) of all-cause mortality, all-CV death, and fatal CHD among patients with gout compared with patients without gout observed by Choi et al are shown in Figure 3.b.

Figure 3.b Increased Risk of All-Cause Mortality, All-CV death, and Fatal CHD Associated With Gout: Multivariable Relative Risk (95% CI) of Death in Patients With Gout



Choi et al [17].
CHD: coronary heart disease; CV: cardiovascular.

Furthermore, Stack et al, also observed similar results. Rates of CV mortality and all-cause mortality in patients with gout compared with patients without gout were 2.31 vs 0.45 per 100 PY and 3.99 vs 1.03 per 100 PY, respectively [19].

Another serious condition associated with gout is renal disease. It is estimated that more than 70% of patients with gout have some degree of renal impairment [16]. This is clinically relevant since coexisting renal impairment has implications in treating gout appropriately. Moreover, the burden of hyperuricemia is strongly associated with risk of renal disease [20-25]. sUA levels >8.5 mg/dL are associated with a >8-fold increase in the risk of renal failure relative to moderate sUA levels (5.0-6.4 mg/dL) [23,26].

3.3 Treatment Landscape

Nonpharmacologic (lifestyle) and risk-reduction measures including patient education, dietary alterations and restrictions, and avoidance of triggers for acute flares (eg, alcohol, diuretics, meals rich in purines) are commonly recommended in the management of gout in patients. Treatment and prevention of gout has traditionally involved anti-inflammatory medication for acute attacks (eg, colchicine, corticosteroids, or NSAIDS). Ultimately in most patients with gout, optimal gout outcome is likely to be dependent on the introduction and long-term use of ULT.

To achieve the treatment goals for gout, the ACR gout guidelines recommend that ULT targets sUA <6.0 mg/dL for most gout patients, and sUA <5.0 mg/dL for patients with tophaceous disease or more severe gout [6].

ULTs can be grouped into 3 categories on the basis of their mechanism of action:

- XOIs: reduce uric acid production (febuxostat, allopurinol).
- Uricosurics: promote urinary uric acid clearance (probenecid, lesinurad).
- Recombinant uricase: a biological agent that enzymatically degrades circulating uric acid (pegloticase).

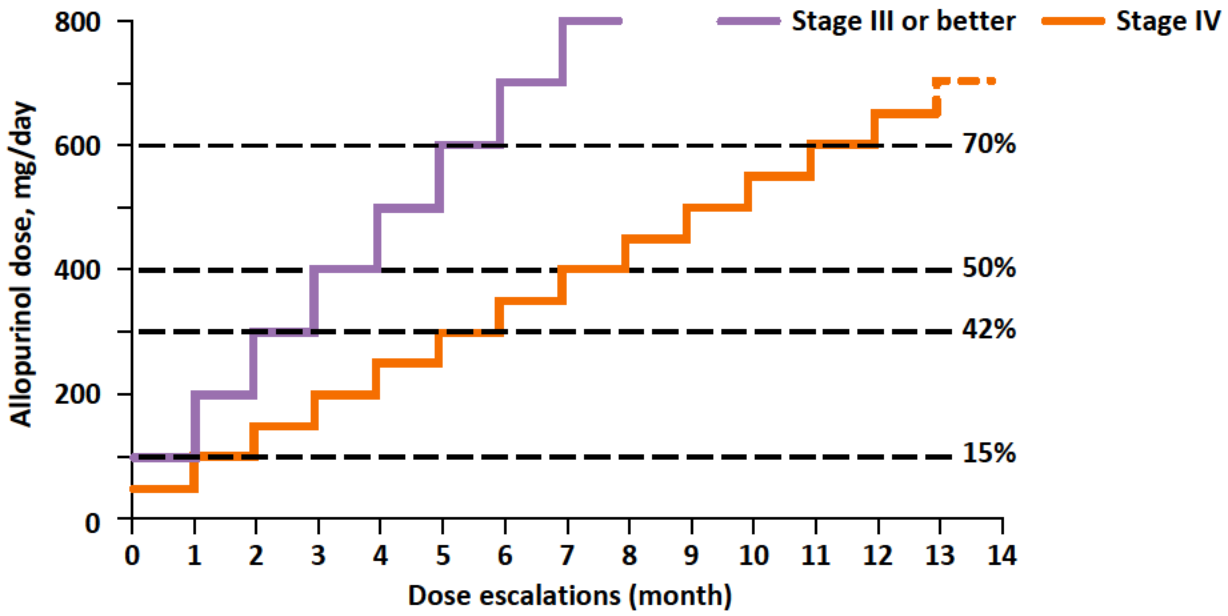
In clinical practice, XOIs are recommended first-line ULT, a role most often fulfilled with allopurinol, or alternatively febuxostat. In the event of failure to reach target urate level with a XOI or intolerance, recommended second-line therapies are combination XOI/uricosuric therapy with lesinurad (200 mg/day only) or probenecid. Alternatively, second-line therapy also includes probenecid monotherapy in doses titrated to urate target. Biological uricolytic intravenous (IV) infusion therapy with pegloticase is third-line therapy and is reserved for patients with clinically far advanced gout and failure or intolerance to alternative ULT. These prescribing practices are also reflected in the 2013 to 2017 QuintilesIMS Health longitudinal patient level data (reported July 2017), which show that allopurinol is prescribed in 92% of the patients and febuxostat is prescribed in 7%; the remaining 1% are other therapies.

Overall, there are only a few ULTs available and each agent has limitations and safety risks.

Allopurinol was approved in the US in 1966 for management of patients with signs and symptoms of primary or secondary gout at a dose range of 100 to 800 mg daily. Allopurinol and its major active metabolite, oxypurinol, are purine-base analogs and relatively nonselective in their actions. They are converted to derivatives that affect other enzymes in purine and pyrimidine metabolism [27].

The most commonly prescribed daily dose range is 100 to 300 mg despite evidence that sUA levels <6.0 mg/dL are achieved in less than 50% of patients receiving 300 mg of allopurinol [28-33]. Fewer than 5% of patients receive allopurinol doses above 300 mg/day [34-36]. In patients with renal impairment, optimal dosing is complicated because of its elimination via the kidneys [27,37]. The US prescribing information carries a precaution that patients with decreased renal function require lower doses of allopurinol than those with normal renal function and these patients should be closely monitored [27]. The ACR gout management guidelines recommend that the initial dose of allopurinol should never exceed 100 mg (and less in patients with impaired renal function), and the dose should be titrated upward in similarly low-dose increments and monitored by measuring sUA to reach target [6]. An example of this up-titration is illustrated in Figure 3.c.

Figure 3.c 2012 ACR Allopurinol Dosing Schedules According to Renal Function



ACR: American College of Rheumatology; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; sUA: serum uric acid.
Stage III: chronic kidney disease (CKD) defined as eGFR 30 to 59 mL/min/1.73 m²; Stage IV: CKD defined as 5 to 30 mL/min/1.73 m².
Dashed lines represent percentage of allopurinol-treated patients reaching target sUA <6.0 mg/dL at allopurinol dose (y-axis).

Recent evidence has shown the safe and effective use of allopurinol in achieving target serum urate levels with careful dose titration. Nevertheless, this approach requires multiple serum urate determinations and dosing changes [6,30,38,39].

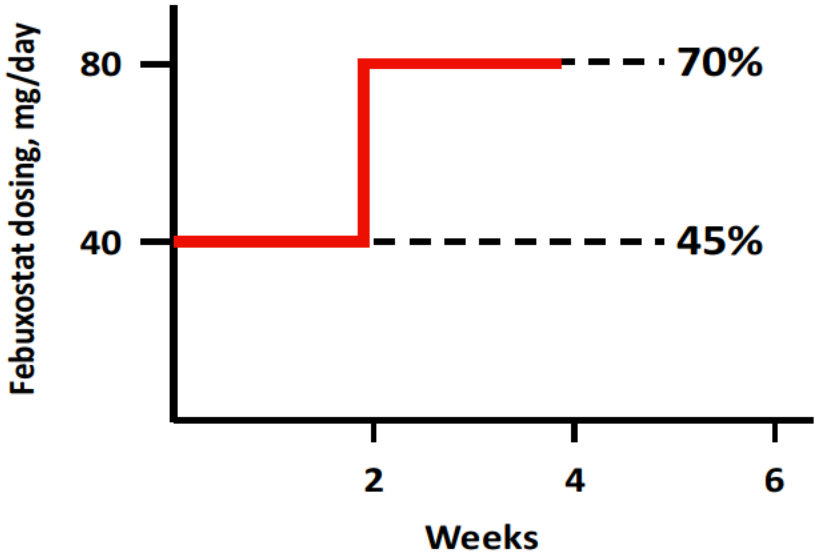
The use of allopurinol is also limited by safety concerns, such as serious hypersensitivity reactions. Among allopurinol-induced rashes, allopurinol hypersensitivity syndrome (AHS) is the most severe or life-threatening [28,29,40-43]. The incidence of AHS in the US is approximately 1:1000; the incidence is reported to be higher in Asian and African American populations [44,45]. The mortality rate in AHS has been reported to be between 20% and 25% [46,47]. Per label, allopurinol also has many drug-drug interactions (DDIs), including dicumarol, sulfinpyrazone, mercaptopurine, azathioprine, ampicillin, amoxicillin, and thiazide diuretics [27].

Febuxostat was approved in the US in February 2009 for the chronic management of hyperuricemia in patients with gout at doses of 40 and 80 mg QD. Febuxostat is a 2-arylthiazole derivative and is a potent, nonpurine, selective XOI that exhibits antihyperuricemic activity by reducing the formation of uric acid. Febuxostat has been shown to potently inhibit both the oxidized and reduced forms of xanthine oxidase [48].

Febuxostat is eliminated almost entirely by liver metabolism via conjugation with uridine diphosphate or oxidation via the cytochrome P-450 system. Since <4% of orally administered febuxostat is eliminated in the urine as unchanged drug, renal impairment is not expected to have a major impact on the elimination of febuxostat from the plasma. Hence, no dose adjustment is necessary when administering febuxostat in patients with mild (eGFR 60 to 89 mL/min) or moderate renal impairment (eGFR 30 to 59 mL/min). Febuxostat 40 mg QD is approved for use in severe renal impairment (eGFR 15 to 29 mL/min) [7].

Febuxostat 40 mg is most often prescribed with a 1-step titration to 80 mg to achieve urate goals. The recommended febuxostat dosing scheme is shown in Figure 3.d.

Figure 3.d Recommended Dosing of Febuxostat Regardless of Renal Function



Dashed lines represent percentage of febuxostat-treated patients reaching target serum uric acid <6.0 mg/dL at febuxostat dose (y-axis).

The US prescribing information includes a Warnings and Precautions for CV events, noting that a higher rate of CV thromboembolic events was observed in subjects treated with febuxostat compared with allopurinol and recommending monitoring for signs and symptoms of MI and stroke [7]. The febuxostat PI also includes Warnings and Precautions regarding gout flare, hepatic effects, and serious skin reactions. Febuxostat is contraindicated in patients being treated with azathioprine or mercaptopurine.

Lesinurad (Zurampic) is a uricosuric agent approved in the US in 2015 for treatment of hyperuricemia associated with gout in patients who have not achieved target sUA levels with a XOI alone. It acts by its inhibitory effects on the renal tubular reabsorptive transporters URAT1 (urate transporter 1) and OAT4 (organic anion transporter 4). The package insert for lesinurad includes a black-box warning that acute renal failure is more common when lesinurad is used without a concomitant XOI. Therefore, lesinurad is only approved for concurrent use with an

XOI. Lesinurad is contraindicated in patients with eCrCl <30 mL/min, and it should not be initiated in patients with an eCrCl <45 mL/min [49].

Probenecid is a uricosuric agent approved in the US in 1951 for treatment of the hyperuricemia associated with gout and gouty arthritis. It is not frequently used as urate-lowering monotherapy in patients with gout, likely because of inadequate efficacy and the potential for kidney stone formation in moderate or more severe renal impairment, inconvenient 3- to 4-times daily dosing regimen, multiple DDIs, and the availability of XOIs [50].

Pegloticase, a pegylated recombinant modified mammalian uricase, was approved in the US in 2010 for treatment of chronic gout in adult patients who are refractory to conventional therapy. It is administered biweekly by IV infusion. The pegloticase package insert carries a black-box warning in the US for infusion reactions, anaphylaxis, and G6PD (glucose-6-phosphate dehydrogenase) deficiency-associated hemolysis and methemoglobinemia. It requires administration in healthcare settings by HCP who are prepared to manage anaphylaxis and infusion-related reactions. Due to the development of high titers of antipegloticase antibodies, it also has the potential to lose urate-lowering effectiveness [51].

Despite what is known about the benefits of ULT, many barriers to treatment remain including:

- There is often a lag time of a year or more to achieve the clinical benefits of reduction in gout flare frequency and tophus resolution.
- The process of breaking down urate crystals often leads to treatment-initiated flares. Multiple flare recurrence is observed in early months of ULT in 40% to 50% of patients.
- The need for dose titration creates a barrier to effective care. Dose titration requires frequent sUA monitoring, resulting in frequent clinic visits and multiple blood sample collection.
- Patient adherence is a challenge. This is likely due to a difficult dose-titration period and the occurrence of treatment-initiated gout flares that may discourage the patient from continuing treatment.

Research into innovative therapies in the field of gout is limited, and the considerations described above highlight the limited options available for patients who suffer from gout.

4.0 CARES STUDY

4.1 Overview

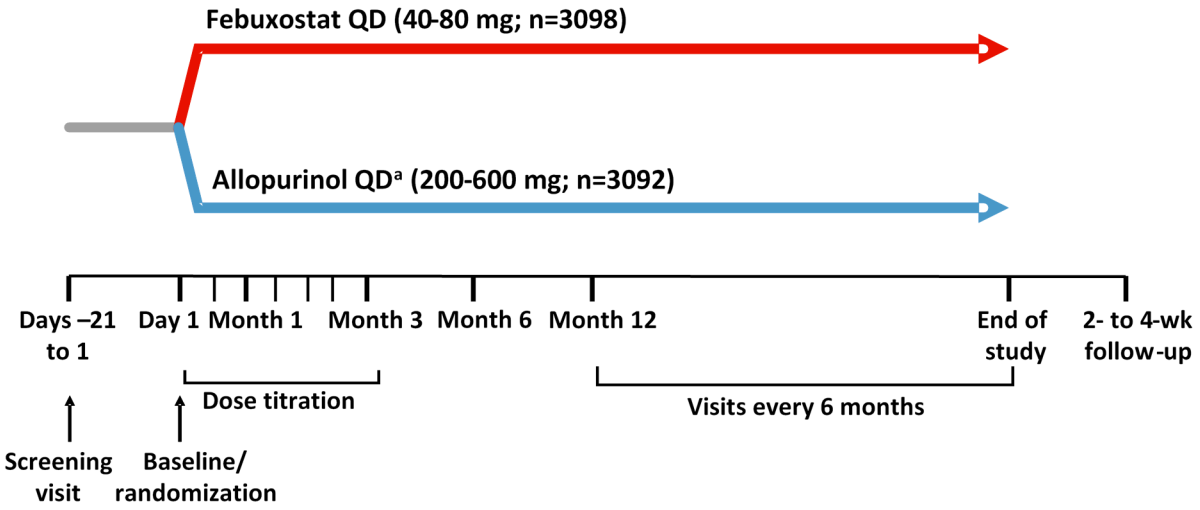
CARES is the first phase 3b multicenter, randomized, double-blind, active-controlled, CVOT of urate lowering drugs in subjects with gout and major CV or cerebrovascular disease. To accrue sufficient number of events in a timely manner, the study was conducted in subjects with gout who had a high CV risk profile. It was designed to assess if febuxostat was noninferior to allopurinol at doses titrated to achieve target sUA <6.0 mg/dL for the primary endpoint of the MACE composite (CV death, nonfatal MI, nonfatal stroke, and unstable angina with urgent coronary revascularization) in subjects with gout and significant CV comorbidities. It included a prespecified noninferiority margin for the HR of <1.3 for the primary endpoint, consistent with the FDA guidance for CVOT conducted for diabetes therapies [52].

The study protocol was finalized following discussions and agreement with FDA. The study design [8] and results [9] have been detailed in peer-reviewed, published journal articles.

4.2 Study Design

A total of 320 study sites (275 in the US, 12 in Canada, and 33 in Mexico) randomized subjects in the double-blind treatment period. A total of 3098 and 3092 subjects were randomized and received at least 1 dose of febuxostat or allopurinol, respectively. It was an event-driven study designed to accrue 624 MACE. Randomization was stratified on the basis of baseline renal function: subjects with normal renal function or mild renal impairment (eCrCl ≥60 mL/min) versus subjects with moderate renal impairment (eCrCl 30 to 59 mL/min). The study included subjects with a history of gout and major CV or cerebrovascular disease including at least 1 of the following: MI, hospitalized unstable angina, cardiac or cerebrovascular revascularization procedure, stroke, hospitalized transient ischemic attack (TIA), peripheral vascular disease, or a history of diabetes mellitus with evidence of micro- or macro-vascular disease. The complete inclusion and exclusion criteria are listed in Appendix 1.

Figure 4.a CARES Study Design



QD: once daily.
[a] Adapted from White et al [9].

Subjects were screened at Day -7 for entry. At the Day 1/randomization visit, eligible subjects were randomized in a 1:1 ratio to receive either febuxostat QD or allopurinol QD.

Subjects randomized to febuxostat initially received 40 mg QD. Subjects remained on 40 mg for the remainder of the study if their sUA was <6.0 mg/dL at the Week 2 Visit. If their sUA was ≥6.0 mg/dL at the Week 2 Visit, they received febuxostat 80 mg QD at Week 4 visit, and remained on this dose for the remainder of the study. No dose adjustment was made with febuxostat on the basis of renal function.

Subjects with normal renal function or mild renal impairment randomized to allopurinol initially received allopurinol 300 mg QD. The dose was increased in 100 mg increments monthly until either an sUA <6.0 mg/dL or an allopurinol dose of 600 mg QD was achieved. Subjects with moderate renal impairment randomized to allopurinol initially received allopurinol 200 mg QD. The dose was increased in 100 mg increments monthly until either an sUA <6.0 mg/dL or an allopurinol dose of 400 mg QD was achieved.

To ensure the blinding of study medication, all study drug medications were over-encapsulated to be identical in appearance. Subjects orally self-administered 2 capsules (study drug, placebo) each morning in the appropriate combination for their assigned dose and treatment.

sUA levels were unblinded to the investigator and Takeda through the Week 10 visit of the study to facilitate dose increases based on sUA response. After the Week 10 visit sUA measurements were blinded to Takeda and the investigator. All dose titrations were completed by the Month 3 visit.

All subjects had a visit at Months 3 and 6. Subsequent study visits were scheduled at Month 6 and at every 6 months thereafter.

Full details on the up-titration of dose can be found Appendix 2. All subjects received gout flare prophylaxis for the first 6 months of the study medication treatment period.

Subjects who discontinued study drug had the option to: (1) continue study participation (off study drug) until the study was completed, or (2) discontinue completely from the study. Subjects who discontinued study drug were strongly encouraged to continue participation until the study was completed.

The study was conducted according to the principles of the International Conference on Harmonization Tripartite Guideline for Good Clinical Practice and was only initiated after review and approval of the relevant ethics committees, institutional review boards, and regulatory authorities. The first subject in the study was enrolled in April 2010 and the last subject in July 2016. The last subject completed the last visit in May 2017.

4.3 Governance Structure

4.3.1 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) was established to evaluate the safety data at specified intervals (ie, every 6 months) and at 3 planned interim analyses. On the basis of these reviews, the DMC could make recommendations to Takeda, including options such as: (1) continue the study, (2) stop the study, or (3) make modifications to the protocol because of safety concerns.

4.3.2 CEC

To ensure the reliable and consistent assessment of CV endpoints, an independent CEC, consisting of 3 clinician experts with experience and training appropriate for reviews of serious cardiac and cerebrovascular events, was established. The CEC prospectively reviewed and adjudicated all suspected CV events and deaths in a blinded fashion to determine if the reported event met the criteria for the components of the primary endpoint and several secondary endpoints. Cause of death was prospectively adjudicated as well. Each death and all serious CV adverse events, including any medically significant updates, were sent by an independent group within a clinical research organization to the CEC for adjudication using an electronic platform. The definitions and adjudication process were defined by the CEC charter and are provided in White et al [9].

The CEC members were not involved in the conduct of any of the febuxostat clinical studies or in any direct discussions with the DMC.

4.4 Statistical Analysis

The primary endpoint was the time from randomization to the first occurrence of any event in the predefined MACE composite (CV death, nonfatal MI, nonfatal stroke, or unstable angina with urgent coronary revascularization).

Secondary endpoints were the time from randomization to the occurrence of each individual event in the predefined MACE composite and the time from randomization to the first occurrence of a composite of CV death, nonfatal MI, or nonfatal stroke.

The time from randomization to all-cause death was included as an additional endpoint.

All endpoints were analyzed using the mITT population, defined as all subjects who were randomized and received at least 1 dose of double-blind study medication.

For the primary MACE composite endpoint, a Cox proportional hazard (CPH) model was used to fit the time to the first occurrence of any event in the composite. Computation of HR (febuxostat vs allopurinol) for the primary endpoint was based on estimated hazard rates for febuxostat and allopurinol. The febuxostat treatment group was compared to the allopurinol treatment group to test for noninferiority in the MACE composite rate using a CPH model with treatment as factor in the model and baseline renal function as a stratification factor.

Noninferiority of febuxostat to allopurinol was to be declared (at an interim or at the final analysis) if the current upper 1-sided CI for the HR was <1.3, calculated with critical values obtained using the Lan-DeMets-O'Brien-Fleming alpha spending function, which preserves an overall 1-sided false-rejection rate of 2.5%. Type 1 error control and assessment of noninferiority were done only for the primary endpoint.

Survival analysis using the CPH model was also performed on: (1) the time to the first occurrence of the composite of CV death, nonfatal MI and nonfatal stroke, (2) the time to first occurrence of each individual event in the predefined MACE composite, and (3) the time to all-cause death. Parameter estimates and 2-sided 95% CIs for the HR were computed.

In addition to the mITT analysis, 2 sensitivity analyses on the primary endpoint were performed related to the timing of events. The first, which was prespecified in the statistical analysis plan (SAP), excluded MACE that occurred more than 30 days after treatment discontinuation. The second, which was not prespecified in the SAP, included only MACE that occurred while subjects were on study drug. Similar sensitivity analyses related to the timing of events were performed for the secondary endpoints and for all cause death.

The number and percentage of subjects with predefined MACE were summarized within the levels of subgroup variables. The prespecified subgroup variables included: baseline renal function, age, sex, body mass index, NSAIDs use, low-dose aspirin use, smoking history, baseline sUA, and history of diabetes, hypertension, nonfatal MI, or nonfatal stroke. The following subgroups were also explored post hoc: race, years since gout diagnosis, hyperlipidemia, history of congestive heart failure (CHF), history of cardiac revascularization, initial gout flare prophylaxis medication, and 3 postrandomization subgroups (colchicine use

during study, insulin use during study, and whether subjects had at least 1 study drug dose increase).

The RR (febuxostat versus allopurinol) and its 95% CI based on the normal approximation were calculated within the levels of each subgroup variable. Homogeneity among the levels of the subgroup variables was assessed using the Cochran-Mantel-Haenszel test. Similar subgroup analyses were also performed for the CV death and all-cause death endpoints using the same set of potential risk factors that were examined for the primary MACE endpoint.

A minimum of 624 MACE was required to provide 90% power to meet a noninferiority margin of 1.3 for the HR (febuxostat relative to allopurinol) of the primary endpoint. The sample size calculation assumed a true HR of 1.0 at a 1-sided 2.5% significance level with 3 interim analyses based on critical values obtained using the Lan DeMets-O'Brien-Fleming alpha spending function.

4.5 Interim Analyses

An independent statistician performed prospective unblinded interim analyses and provided the results to the DMC. Interim analyses were conducted when approximately 25%, 50%, and 75% of the events occurred, followed by a final analysis. Four approximately equally-spaced analyses and a 1-sided overall significance level of 0.025 were used, with the Lan-DeMets alpha spending approach with an O'Brien-Fleming stopping boundary.

At any interim analysis, if the upper confidence limit of the HR was <1.3, noninferiority of febuxostat relative to allopurinol regarding CV risk would be declared and the DMC could recommend stopping the study.

Following the 25%, 50%, and 75% interim analyses in July 2013, January 2015, and April 2016, respectively, the DMC recommended that Takeda continue the study without modification.

At the DMC meeting in October 2016, the DMC informed the Takeda representatives that the noninferiority criterion for the primary endpoint had been met at the 75% interim analysis conducted in April 2016, meeting the criteria for stopping the study early. The DMC explained that the April 2016 recommendation to continue the study until the full 624 events occurred was based on an observed imbalance between the HR for death from all causes and CV death in the mITT analysis (elevated) and in the analysis of events that occurred while on treatment (not elevated). They also recommended that Takeda inform FDA of these findings.

As it was important to maintain the integrity of the ongoing study and ensure controlled and limited access to this information, Takeda formed an unblinded team. This team included the Takeda representatives who was informed of the unblinded results at the October 2016 DMC meeting. Access was controlled by a confidentiality agreement that included a Data Access Management Plan and a roster of the unblinded team was maintained. Members of the unblinded team did not participate in the ongoing conduct and management of the study until final database lock and final study unblinding was achieved.

On November 2016, the results from the 75% interim analysis were sent to a single unblinded reviewer at the FDA. In December 2016, FDA deferred any change in the study conduct to

Takeda and the DMC. On the basis of the recommendation of the DMC, Takeda continued the CARES study until the full 624 events occurred.

On the basis of the group sequential design, the 75% interim analysis was considered the primary analysis for the primary MACE endpoint for statistical inference. Except for the primary analysis of the primary endpoint, all other analyses of the study were based on the final analysis at the completion of the study. An analysis for the primary endpoint based on the final accrual of MACE was also conducted to provide additional supportive evidence for the primary endpoint.

4.6 Overall Exposure and Disposition

4.6.1 Exposure

A total of 3098 and 3092 subjects were randomized and received at least 1 dose of febuxostat or allopurinol, respectively. The mean duration of study drug exposure in the febuxostat and allopurinol groups was 892 days and 880 days, respectively in the double-blind treatment period of the study. Cumulative duration of exposure was similar between febuxostat and allopurinol treatment groups, with 70% and 70% of subjects, respectively, with at least 1 year of exposure; 36% and 35%, respectively, with at least 3 years of exposure; and 15% and 14%, respectively, with at least 5 years of exposure.

Subjects who had discontinued study drug but had not withdrawn consent continued to be followed in the study. The mean duration of study participation in the febuxostat and allopurinol groups was 1079 days and 1070 days, respectively. Cumulative duration of study participation was similar between treatment groups, with 82%, 46%, and 20%of subjects in each treatment group with at least 1, 3, and 5 years of participation, respectively.

4.6.2 Final Titrated Dose

As described in the study design, the initial dose received for each treatment group was up titrated if sUA <6.0 mg/dL was not achieved. In the febuxostat group, 61% of subjects remained on their starting dose of 40 mg (Table 4.a). In the allopurinol group, 52% of subjects remained on their starting dose. The most common final titrated dose for the allopurinol group was 300 mg (45% of subjects) and only 4% each of subjects had final titrated doses of 500 and 600 mg.

Table 4.a Final Titrated Treatment Dose Overall and by Renal Function

	Final Dose						
	Febuxostat [a] n (%) N = 3098			Allopurinol [b] n (%) N = 3092			
Renal Function	**40 mg**	**80 mg**	**200 mg**	**300 mg**	**400 mg**	**500 mg**	**600 mg**
Moderately impaired	969 (59.2)	667 (40.8)	669 (41.0)	459 (28.1)	500 (30.7)	2 (0.1) [c]	1 (<0.1) [c]
Mildly impaired	756 (62.1)	461 (37.9)	4 (0.3)	772 (62.7)	238 (19.3)	115 (9.3)	102 (8.3)
Normal	159 (66.5)	80 (33.5)	0	148 (64.9)	40 (17.5)	15 (6.6)	25 (11.0)
All	1890 (61.0)	1208 (39.0)	674 (21.8)	1380 (44.6)	778 (25.2)	132 (4.3)	128 (4.1)

eCrCl: estimated creatine clearance; sUA: serum uric acid.
Moderate renal impairment: eCrCl 30 to 59 mL/min; mild renal impairment: eCrCl 60 to 89 mL/min; normal renal function: eCrCl ≥90 mL/min.
[a] Titration of febuxostat dose was based on sUA.
[b] Titration of allopurinol dose was based on sUA and renal function.
[c] Subjects inadvertently received 500 mg and 600 mg.

4.6.3 Disposition

Subject study drug disposition is shown in Table 4.b.

At the end of the study, 43% of subjects overall were on study drug, with similar rates in the febuxostat and allopurinol treatment groups (43% vs 44%, respectively). The reasons for premature discontinuation of study drug were similar between the treatment groups.

Table 4.b CARES Subjects Study Drug Disposition

	Subjects, n (%)	
	Febuxostat	**Allopurinol**
Randomized, N	3101	3097
Randomized but did not take study drug, n [a]	3	5
On drug at study end	1324 (42.7)	1365 (44.1)
Prematurely discontinued study drug	1777 (57.3)	1732 (55.9)
Reason for study drug discontinuation		
Voluntary withdrawal	699 (22.5)	670 (21.6)
Adverse events	453 (14.6)	446 (14.4)
Other	300 (9.7)	321 (10.4)
Lost to follow-up	214 (6.9)	205 (6.6)
Major protocol deviation	111 (3.6)	90 (2.9)

[a] Excluded from the modified intent-to-treat population.

Subject study visit disposition is shown in Table 4.c.

Subjects who discontinued study drug had the option to continue study participation without study drug treatment.

Overall, 3410 subjects had completed all planned study visits (55% of total subjects) at the end of the study, with similar percentages in the febuxostat and allopurinol groups (55% in both groups). Generally, the reasons for study visit discontinuation were similar between treatment groups.

Table 4.c CARES Subjects Study Visit Disposition

	Subjects, n (%)	
	Febuxostat	**Allopurinol**
Randomized, N	3101	3097
Completed study visits	1704 (55.0)	1706 (55.1)
Discontinued study visits	1397 (45.0)	1391 (44.9)
Reason for study visit discontinuation		
Voluntary withdrawal	595 (19.2)	587 (19.0)
Other	333 (10.7)	363 (11.7)
Lost to follow-up	226 (7.3)	223 (7.2)
Adverse events	191 (6.2)	172 (5.6)
Major protocol deviation	52 (1.7)	46 (1.5)

4.6.4 Subject Retention Measures

From the beginning of the study, a recruitment and retention program was implemented to engage and support study subjects. Takeda's efforts were augmented by use of specialized clinical subject recruitment vendors (eg, Acurian) who engaged with sites to focus on subject communication and study engagement. Throughout the study, study monitors encouraged sites to retain subjects in the study, including those subjects who had chosen to discontinue study drug. Study coordinator workshops were held to engage site staff and to discuss challenges encountered and share best practices. During the workshops, sites' staff were trained on available tools and strategies that could be helpful in retaining subjects. Takeda held a motivational meeting for the principal investigators to draw on their collective experience regarding challenges in recruiting and retaining subjects. One challenge encountered was the increase of gout flares during the first year of ULT; therefore, a gout flare education program was developed to assist the sites in educating subjects on the importance of continuing treatment if they experience gout flares. To retain subjects in the study, a licensed private investigation agency (OmniTrace, Inc) was contracted to assist US sites in locating subjects with whom the sites lost contact and, therefore, were considered lost to follow-up. Once located, these subjects were encouraged to resume their study visits or complete an end-of-study visit.

4.6.5 Collection of Vital Status

In addition to contracting OmniTrace for subject retention measures as described in Section 4.6.4, OmniTrace was also contracted to determine vital status toward the end of the study (before study unblinding). Any subject who, despite previous efforts, remained lost to follow-up or who had early terminated the study (excluding those known to have died) were included in the collection of vital status information. Sites had to complete a form with the last known subject contact information, which was then forwarded to OmniTrace. OmniTrace used a variety of

search mechanisms which varied by country. These included but were not limited to: death index in the US, obituaries, and social media. The deaths identified during this search were not adjudicated by the CEC. The scope of this vital status collection included 2352 subjects. Vital status was obtained for 87% of subjects in the study (86% febuxostat and 87% allopurinol), including 199 additional deaths (febuxostat n = 89 and allopurinol n = 110); vital status could not be obtained for 822 subjects (13% of randomized subjects). The reasons for not obtaining vital status included: site did not provide contact information to OmniTrace (n = 698) and search was unable to confirm an alive/dead status (n = 124).

4.7 Demographic and Other Baseline Characteristics and Concomitant Medications

Baseline and demographic characteristics were similar between treatment groups. As typical of the gout population and similar to the febuxostat phase 3 randomized-controlled studies, most subjects were male (84%) and white (69%); the overall mean age was 65 years. Over half in each treatment group had moderate renal impairment (eCrCl 30 to 59 mL/min). Both groups had similar gout history, with mean time since initial gout diagnosis ~12 years and mean sUA ~8.7 mg/dL.

Most subjects (62%) had a history of ULT, which was similar between treatment groups. The most common prior ULT was allopurinol (56% of all subjects), which was higher compared with febuxostat (4% of all subjects).

Unlike the febuxostat phase 3 randomized controlled studies, the study population of CARES was enriched by enrolling hyperuricemic subjects with gout who had a high CV risk profile. No meaningful differences with respect to history of CV disease were noted between the treatment groups. The most common CV histories were prior MI, coronary revascularization, hospitalized unstable angina, and diabetes with vascular disease.

The most common concomitant medications used (by therapeutic class) were those that are typical in a population with CV disorders. Overall, the most common medications taken, based on therapeutic class, were lipid-modifying agents (74%); agents acting on the renin-angiotensin system (70%); beta-blocking agents (59%); drugs used in diabetes (47%); diuretics (41%); and cardiac therapy (25%). No notable difference in concomitant medication use by therapeutic class was observed between treatment groups

Full summaries of demographic and other baseline characteristics are provided in Appendix 3.

4.8 CV Outcomes

4.8.1 Primary Endpoint: MACE Composite

As described in Section 4.5, the criterion to declare noninferiority of febuxostat relative to allopurinol for the primary endpoint was met at the 75% interim analysis. As such, it was considered the primary analysis for the primary MACE endpoint for statistical inference; the final analysis is considered a sensitivity analysis for the primary endpoint. The results from the 75% interim analysis along with the final analysis are summarized in Table 4.d.

The results for the primary endpoint from the final analysis are consistent to those observed in the primary analysis at the 75% interim analysis.

All other analyses of the study that follow are based on the final analysis.

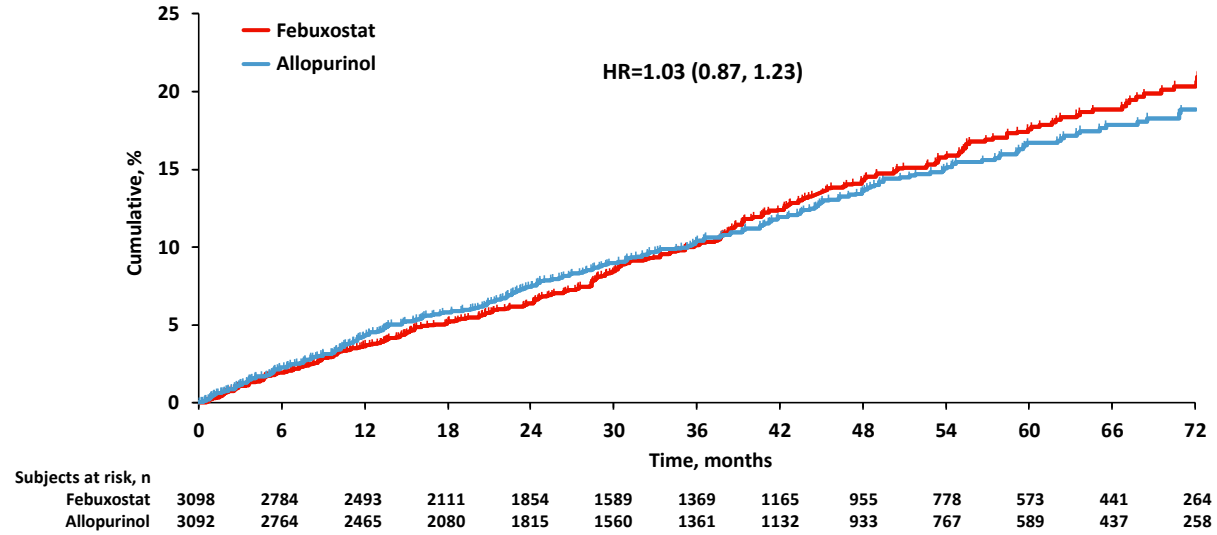
Table 4.d Adjudicated MACE Composite: Primary Analysis (75% Interim) and Final Analysis of Primary Endpoint (mITT)

	Subjects, n (%)		
	Febuxostat N = 3098	**Allopurinol N = 3092**	**Hazard Ratio [a] (Upper Bound CI)**
75% interim analysis (primary analysis) [b]	244 (8.0)	244 (8.0)	0.99 (1.23)
Final analysis	335 (10.8)	321 (10.4)	1.03 (1.23) [*]

MACE: major adverse cardiac event; mITT: modified intent-to-treat.
[*] P = 0.002 for noninferiority [9].
[a] Febuxostat to allopurinol.
[b] Febuxostat N = 3039, allopurinol N = 3034.

The results from the final analysis of the primary MACE composite are summarized in the Kaplan-Meier Plot in Figure 4.b.

Figure 4.b Kaplan-Meier Plot of Time to First Occurrence of MACE Composite: Final Analysis (mITT)



MACE: major adverse cardiac event; mITT: modified intent-to-treat.

The additional sensitivity analyses for the primary endpoint (MACE composite) on drug and on-drug plus 30 days after drug discontinuation were consistent with the primary analysis at the 75% interim analysis and at the final analysis.

Table 4.e Summary of Sensitivity Analysis for the Primary Endpoint (mITT)

	Subjects, n (%)		
MACE	**Febuxostat N = 3098**	**Allopurinol N = 3092**	**Hazard Ratio [a] 95% Adjusted CI**
mITT analysis	335 (10.8)	321 (10.4)	1.03 (0.87, 1.23)
On drug	191 (6.2)	199 (6.4)	0.94 (0.76, 1.17)
On drug plus up to 30 days post	242 (7.8)	238 (7.7)	1.00 (0.82, 1.22)

MACE: major adverse cardiac event; mITT: modified intent-to-treat.
mITT analysis includes all events; up to 30 days post includes all events occurring up to 30 days posttreatment; on drug analysis includes only events occurring while receiving study drug.
[a] Febuxostat to allopurinol.

The results for the planned and ad hoc subgroup analyses were consistent to the mITT analysis. No heterogeneity was observed for the primary MACE composite endpoint on the basis of demographic, baseline characteristics, and postbaseline characteristics. The results from the subgroup analyses are shown in Figure 4.c.

Figure 4.c Risk Ratios (95% CI) for Primary MACE Composite Endpoint by Subgroups

Baseline variables		Subjects, n/N		MACE, %		Favors	RR (95% CI)	Interaction P value
		Febuxostat	Allopurinol	Febuxostat	Allopurinol	← Febuxostat Allopurinol →		
Overall mITT analysis		**335/3098**	**321/3092**	**10.8**	**10.4**		**1.04 (0.90, 1.20)**	
Age, yr	<65	133/1584	130/1506	8.4	8.6		0.97 (0.77, 1.23)	0.380
	≥65	202/1514	191/1586	13.3	12.0		1.11 (0.92, 1.33)	
Gender	Female	42/494	45/500	8.5	9.0		0.94 (0.63, 1.41)	0.607
	Male	293/2604	276/2592	11.3	10.6		1.06 (0.90, 1.23)	
BMI, kg/m^2	<30	110/1045	106/1063	10.5	10.0		1.06 (0.82, 1.36)	0.886
	≥30	225/2053	215/2024	11.0	10.6		1.03 (0.86, 1.23)	
Race	White	268/2160	260/2140	12.4	12.1		1.02 (0.87, 1.20)	0.652
	Non-white	67/938	61/952	7.1	6.4		1.11 (0.80, 1.56)	
Years since gout diagnosis	<5	130/1150	118/1091	11.3	10.8		1.05 (0.83, 1.32)	0.461
	5-10	48/580	60/615	8.3	9.8		0.85 (0.59, 1.22)	
	>10	156/1367	143/1386	11.4	10.3		1.11 (0.89, 1.37)	
Baseline sUA, mg/dL	<9.0	162/1778	166/1815	9.1	9.1		1.00 (0.81, 1.22)	0.779
	9.0-10.0	83/666	71/646	12.5	11.0		1.13 (0.84, 1.53)	
	≥10.0	90/654	84/631	13.8	13.3		1.03 (0.78, 1.36)	
NSAID use	Yes	112/856	95/908	13.1	10.5		1.25 (0.97, 1.62)	0.096
	No	223/2242	226/2184	9.9	10.3		0.96 (0.81, 1.15)	
Low-dose aspirin use	Yes	163/1496	175/1481	10.9	11.8		0.92 (0.75, 1.13)	0.091
	No	172/1602	146/1611	10.7	9.1		1.18 (0.96, 1.46)	
Colchicine used during study	Yes	104/699	84/694	14.9	12.1		1.23 (0.94, 1.61)	0.149
	No	231/2399	237/2398	9.6	9.9		0.97 (0.82, 1.16)	
Initial prophy medication	Colchicine	295/2604	283/2591	11.3	10.9		1.04 (0.89, 1.21)	0.906
	Non-colchicine	40/494	38/501	8.1	7.6		1.07 (0.70, 1.63)	

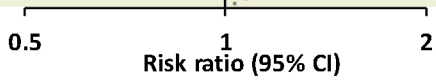


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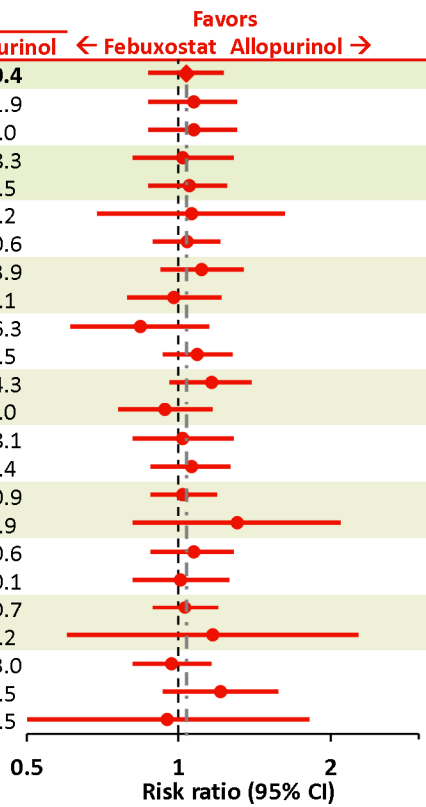
Figure 4.c Risk Ratios (95% CI) for Primary MACE Composite Endpoint by Subgroups (continued)

Baseline variables		Subjects, n/N		MACE, %		RR (95% CI)	Interaction P value
		Febuxostat	Allopurinol	Febuxostat	Allopurinol		
Overall mITT analysis		**335/3098**	**321/3092**	**10.8**	**10.4**	**1.04 (0.90, 1.20)**	
≥1 dose adjustment	Yes	153/1207	176/1485	12.7	11.9	1.07 (0.87, 1.31)	0.974
	No	182/1891	145/1607	9.6	9.0	1.07 (0.87, 1.31)	
Insulin use during study	Yes	116/620	111/607	18.7	18.3	1.02 (0.81, 1.29)	0.906
	No	219/2478	210/2485	8.8	8.5	1.05 (0.87, 1.25)	
Smoking history	Current smoker	38/390	38/415	9.7	9.2	1.06 (0.69, 1.63)	0.915
	Non/ex-smoker	297/2708	283/2677	11.0	10.6	1.04 (0.89, 1.21)	
History of nonfatal MI	Yes	185/1197	171/1231	15.5	13.9	1.11 (0.92, 1.35)	0.373
	No	150/1901	150/1861	7.9	8.1	0.98 (0.79, 1.22)	
History of nonfatal stroke	Yes	63/460	67/410	13.7	16.3	0.84 (0.61, 1.15)	0.152
	No	272/2638	254/2682	10.3	9.5	1.09 (0.93, 1.28)	
History of cardiac revascularization	Yes	187/1129	169/1182	16.6	14.3	1.16 (0.96, 1.40)	0.157
	No	148/1969	152/1910	7.5	8.0	0.94 (0.76, 1.17)	
History of congestive heart failure	Yes	115/622	114/631	18.5	18.1	1.02 (0.81, 1.29)	0.858
	No	220/2476	207/2461	8.9	8.4	1.06 (0.88, 1.27)	
History of hyperlipidemia	Yes	297/2678	294/2702	11.1	10.9	1.02 (0.88, 1.19)	0.329
	No	38/420	27/390	9.0	6.9	1.31 (0.81, 2.10)	
History of diabetes	Yes	193/1710	180/1699	11.3	10.6	1.07 (0.88, 1.29)	0.723
	No	142/1388	141/1393	10.2	10.1	1.01 (0.81, 1.26)	
History of hypertension	Yes	318/2864	306/2851	11.1	10.7	1.03 (0.89, 1.20)	0.734
	No	17/234	15/241	7.3	6.2	1.17 (0.60, 2.28)	
Renal function	Moderate	207/1636	212/1631	12.7	13.0	0.97 (0.81, 1.16)	0.405
	Mild	110/1217	92/1231	9.0	7.5	1.21 (0.93, 1.58)	
	Normal	17/239	17/228	7.1	7.5	0.95 (0.50, 1.82)	



BMI: body mass index; CV: cardiovascular; MACE: major adverse cardiac event; MI: myocardial infarction; mITT: modified intent-to-treat; NSAID: nonsteroidal anti-inflammatory drug; RR: relative risk; sUA: serum uric acid.

4.8.2 Secondary Endpoint: APTC Composite (CV death, Nonfatal MI, and Nonfatal Stroke)

In the analysis of the secondary endpoint of time from randomization to the first occurrence of any APTC event (CV death, nonfatal MI, and nonfatal stroke), the overall percentage of subjects who experienced an APTC event was numerically higher in the febuxostat group than the allopurinol group (Table 4.f).

Table 4.f APTC Composite (CV death, Nonfatal MI, and Nonfatal Stroke): Analysis of Secondary Endpoint (mITT)

	Subjects n (%)		
	Febuxostat N = 3098	**Allopurinol N = 3092**	**Hazard Ratio [a] 95% CI**
APTC composite	296 (9.6)	271 (8.8)	1.09 (0.92, 1.28)
CV death	134 (4.3)	100 (3.2)	
Nonfatal MI	111 (3.6)	118 (3.8)	
Nonfatal stroke	71 (2.3)	70 (2.3)	

APTC: Antiplatelet Trialists' Collaborative; CV: cardiovascular; MI: myocardial infarction; mITT: modified intent-to-treat.
[a] Febuxostat to allopurinol.

4.8.3 Secondary Endpoint: Analysis of Time to Occurrence of Each Event in the MACE Composite

The components of the MACE composite were analyzed as secondary endpoints. The rate of CV death was higher in the febuxostat group, with 4.3% of subjects experiencing an event of CV death, compared with 3.2% in the allopurinol group, with HR 1.34 (2-sided 95% CI 1.03, 1.73) (Table 4.g). The rates of nonfatal MI, nonfatal stroke, and unstable angina with urgent revascularization were numerically similar or lower in the febuxostat group than in the allopurinol group.

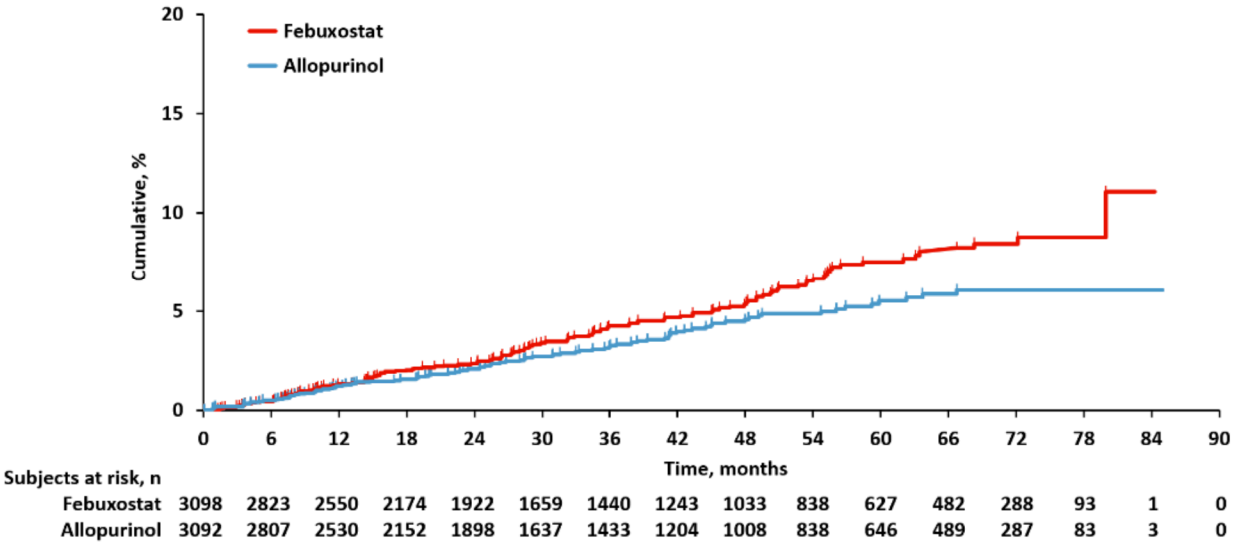
Table 4.g Analysis of MACE and Each Event in the MACE Composite (mITT)

	Subjects n (%)		
	Febuxostat N = 3098	Allopurinol N = 3092	Hazard Ratio [a] (95% CI)
Composite primary endpoint	335 (10.8)	321 (10.4)	1.03 (0.87, 1.23) [b]
CV death	134 (4.3)	100 (3.2)	1.34 (1.03, 1.73)
Nonfatal MI	111 (3.6)	118 (3.8)	0.93 (0.72, 1.21)
Nonfatal stroke	71 (2.3)	70 (2.3)	1.01 (0.73, 1.41)
Unstable angina with urgent coronary revascularization	49 (1.6)	56 (1.8)	0.86 (0.59, 1.26)

Source: White et al [9].
CV: cardiovascular; MACE: major adverse cardiac event; MI: myocardial infarction; mITT: modified intent-to-treat.
[a] Febuxostat to allopurinol.
[b] 95% adjusted CI.

The Kaplan-Meier Plot for time to CV death is shown in Figure 4.d.

Figure 4.d Kaplan Meier Plot of Time to the First Occurrence of CV Death



CV: cardiovascular.

Two sensitivity analyses for CV death on drug and on-drug plus 30 days after drug discontinuation were conducted (Table 4.h).

Many of the CV deaths occurred after the last dose of study drug. In both treatment groups, the sensitivity analysis for on-drug plus 30 days demonstrated a substantially higher number of CV deaths compared with the sensitivity analysis for subjects on drug. This finding is likely due to discontinuation of study drug following the onset of an adverse event that subsequently

progressed into a fatal outcome. Approximately half of the CV deaths in the study occurred more than 30 days after discontinuation of study drug.

Table 4.h Summary of CV Deaths (mITT)

	Subjects, n (%)		
	Febuxostat N = 3098	**Allopurinol N = 3092**	**Hazard Ratio [a] (95% CI)**
mITT	134 (4.3)	100 (3.2)	1.34 (1.03, 1.73)
On-drug	23 (0.7)	14 (0.5)	1.62 (0.84, 3.15)
On-drug plus 30 days	62 (2.0)	41 (1.3)	1.49 (1.01, 2.22)

CV: cardiovascular; mITT: modified intent-to-treat.
mITT analysis includes all events; on-drug plus 30 days includes all events occurring up to 30 days posttreatment; on-drug analysis includes only events occurring while receiving study drug.
[a] Febuxostat to allopurinol.

Rates of CV death by adjudicated cause of CV death are summarized in Table 4.i. During the CARES study, sudden cardiac death was the most prevalent cause of death and the key source of imbalance for overall CV death between the febuxostat and allopurinol treatment groups (2.7% vs 1.8%, respectively).

Sudden cardiac death was defined in the CEC charter as a death that occurred unexpectedly in a previously stable patient and was either witnessed (with or without new or worsening symptoms of a cardiac nature) or unwitnessed with the clinical status of the study participant known within the week preceding death. Using the methodology followed by the CARES study CEC to adjudicate sudden cardiac death is both standard and conservative [53]. Despite best practices by adjudication committees, the etiologies of sudden cardiac death in the adjudication process are not precise [54]. Assigning deaths to the category of sudden cardiac death, etiology unknown is recognized as being associated with multifactorial etiologies, including ischemic events (eg, MI, ventricular arrhythmias) and noncardiac events (eg, respiratory failure, pulmonary embolism, opioid overdose).

In CARES, death due to arrhythmia was comparable between the treatment groups (0.2% for febuxostat and 0.3% for allopurinol) as were nonfatal arrhythmias not associated with ischemia (3.6% for febuxostat and 3.7% for allopurinol) [9]. As shown in Table 4.g, ischemic cardiac events (MI and unstable angina with urgent coronary revascularization) were both numerically lower on febuxostat than on allopurinol and not statistically different between treatment groups. Hence, the findings in the categories of adjudicated nonfatal cardiac events are not in alignment with cardiac causes of sudden cardiac death in the study.

Other causes of CV death had rates of <1.0% in both the febuxostat and allopurinol groups and were comparable in both treatment groups.

Table 4.i Adjudicated Causes of CV Death (mITT)

	Subjects, n (%)	
	Febuxostat N = 3098	**Allopurinol N = 3092**
CV deaths	**134 (4.3)**	**100 (3.2)**
Sudden cardiac death	83 (2.7)	56 (1.8)
Heart failure	20 (0.6)	13 (0.4)
Stroke	8 (0.3)	11 (0.4)
MI	11 (0.4)	6 (0.2)
Cardiac arrhythmia	7 (0.2)	9 (0.3)
Valvular heart disease	3 (<0.1)	2 (<0.1)
Heart and respiratory failure	1 (<0.1)	1 (<0.1)
CV hemorrhage	0	1 (<0.1)
Peripheral arterial disease	0	1 (<0.1)
Other CV deaths	1 (<0.1)	0

CV: cardiovascular, MI: myocardial infarction; mITT: modified intent-to-treat.

To better understand potential factors for the higher rate of CV death in the febuxostat treatment group, planned and ad hoc subgroup analyses were conducted for CV death. Potential risk factors explored included demographic characteristics, baseline medical histories, and differences in use of concomitant medications, including CV medications, insulin, NSAIDs, colchicine, or aspirin. The results from the subgroup analyses are listed and illustrated in Figure 4.e. For most demographic, baseline, and postbaseline characteristics subgroups, the results were generally comparable to those from the overall mITT analysis (Figure 4.c).

Figure 4.e Risk Ratios (95% CI) for CV Death by Subgroups

Baseline variables		Subjects, n/N Febuxostat	Subjects, n/N Allopurinol	CV mortality, % Febuxostat	CV mortality, % Allopurinol	RR (95% CI)	Interaction P value
Overall mITT analysis		**134/3098**	**100/3092**	**4.3**	**3.2**	**1.34 (1.04, 1.72)**	
Age, yr	<65	41/1584	36/1506	2.6	2.4	1.08 (0.70, 1.68)	0.205
	≥65	93/1514	64/1586	6.1	4.0	1.52 (1.12, 2.08)	
Gender	Female	17/494	13/500	3.4	2.6	1.32 (0.65, 2.70)	0.971
	Male	117/2604	87/2592	4.5	3.4	1.34 (1.02, 1.76)	
BMI, kg/m^2	<30	50/1045	37/1063	4.8	3.5	1.37 (0.91, 2.08)	0.863
	≥30	84/2053	63/2024	4.1	3.1	1.31 (0.95, 1.81)	
Race	White	107/2160	77/2140	5.0	3.6	1.38 (1.03, 1.83)	0.636
	Non-white	27/938	23/952	2.9	2.4	1.19 (0.69, 2.06)	
Years since gout diagnosis	<5	63/1150	45/1091	5.5	4.1	1.33 (0.91, 1.93)	0.508
	5-10	15/580	17/615	2.6	2.8	0.94 (0.47, 1.86)	
	>10	56/1367	38/1386	4.1	2.7	1.49 (1.00, 2.24)	
Baseline sUA, mg/dL	<9.0	60/1778	35/1815	3.4	1.9	1.75 (1.16, 2.64)	0.225
	9.0-10.0	28/666	26/646	4.2	4.0	1.04 (0.62, 1.76)	
	≥10.0	46/654	39/631	7.0	6.2	1.14 (0.75, 1.72)	
NSAID use	Yes	41/856	20/908	4.8	2.2	2.17 (1.28, 3.68)	0.032
	No	93/2242	80/2184	4.1	3.7	1.13 (0.84, 1.52)	
Low-dose aspirin use	Yes	49/1496	57/1481	3.3	3.8	0.85 (0.58, 1.24)	0.001
	No	85/1602	43/1611	5.3	2.7	1.99 (1.39, 2.85)	
Colchicine used during study	Yes	35/699	16/694	5.0	2.3	2.17 (1.21, 3.89)	0.062
	No	99/2399	84/2398	4.1	3.5	1.18 (0.89, 1.57)	
Initial prophy medication	Colchicine	119/2604	86/2591	4.6	3.3	1.38 (1.05, 1.81)	0.540
	Non-colchicine	15/494	14/501	3.0	2.8	1.09 (0.53, 2.23)	

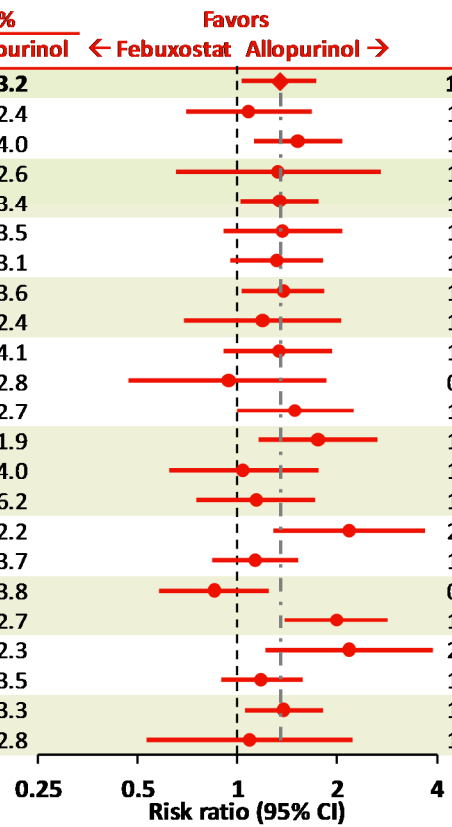


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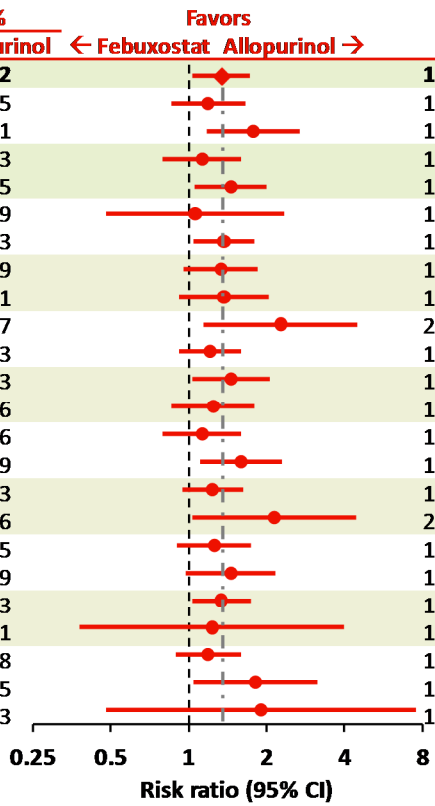
Figure 4.e Risk Ratios (95% CI) for CV Death by Subgroups (continued)

Baseline variables		Subjects, n/N Febuxostat	Subjects, n/N Allopurinol	CV mortality, % Febuxostat	CV mortality, % Allopurinol	RR (95% CI)	Interaction P value
Overall mITT analysis		**134/3098**	**100/3092**	**4.3**	**3.2**	**1.34 (1.04, 1.72)**	
≥1 dose adjustment	Yes	65/1207	67/1485	5.4	4.5	1.19 (0.86, 1.66)	0.146
	No	69/1891	33/1607	3.6	2.1	1.78 (1.18, 2.68)	
Insulin use during study	Yes	44/620	38/607	7.1	6.3	1.13 (0.75, 1.72)	0.373
	No	90/2478	62/2485	3.6	2.5	1.46 (1.06, 2.00)	
Smoking history	Current smoker	12/390	12/415	3.1	2.9	1.06 (0.48, 2.34)	0.547
	Non/ex-smoker	122/2708	88/2677	4.5	3.3	1.37 (1.05, 1.79)	
History of nonfatal MI	Yes	78/1197	60/1231	6.5	4.9	1.34 (0.96, 1.85)	0.955
	No	56/1901	40/1861	2.9	2.1	1.37 (0.92, 2.05)	
History of nonfatal stroke	Yes	28/460	11/410	6.1	2.7	2.27 (1.14, 4.50)	0.090
	No	106/2638	89/2682	4.0	3.3	1.21 (0.92, 1.60)	
History of cardiac revascularization	Yes	71/1129	51/1182	6.3	4.3	1.46 (1.03, 2.07)	0.528
	No	63/1969	49/1910	3.2	2.6	1.25 (0.86, 1.80)	
History of congestive heart failure	Yes	60/622	54/631	9.6	8.6	1.13 (0.79, 1.60)	0.201
	No	74/2476	46/2461	3.0	1.9	1.60 (1.11, 2.30)	
History of hyperlipidemia	Yes	111/2678	90/2702	4.1	3.3	1.24 (0.95, 1.63)	0.169
	No	23/420	10/390	5.5	2.6	2.14 (1.03, 4.43)	
History of diabetes	Yes	76/1710	60/1699	4.4	3.5	1.26 (0.90, 1.75)	0.585
	No	58/1388	40/1393	4.2	2.9	1.46 (0.98, 2.16)	
History of hypertension	Yes	128/2864	95/2851	4.5	3.3	1.34 (1.03, 1.74)	0.888
	No	6/234	5/241	2.6	2.1	1.24 (0.38, 3.99)	
Renal function	Moderate	93/1636	78/1631	5.7	4.8	1.19 (0.89, 1.59)	0.379
	Mild	34/1217	19/1231	2.8	1.5	1.81 (1.04, 3.16)	
	Normal	6/239	3/228	2.5	1.3	1.91 (0.48, 7.54)	



BMI: body mass index, NSAID: nonsteroidal anti-inflammatory, MI: myocardial infarction, mITT: modified intent-to-treat, sUA: serum uric acid.

Heterogeneity was observed in analyses of CV death in 3 subgroups associated with concomitant administration during the study, including low-dose aspirin (defined as <325 mg/day), NSAIDs (ongoing at baseline), and colchicine. The number of events contributing to these differences are small and accompanied by large CIs. These findings may have been due to chance, given the large number of statistical tests performed.

No significant associations were noted for the subgroups with a history of CHF or renal impairment described as follows:

- The presence of CHF, a known predictor of mortality, was examined as a potential risk factor. Among subjects with the presence of CHF, the rate of CV death was higher in both treatment groups compared with subjects without CHF. However, the RR between the treatment groups was lower (1.13) in subjects with a history of CHF compared with subjects without a history of CHF (1.60).
- Given the association of CV mortality with renal impairment, the impact of renal function on CV death was assessed. The rates of CV death were higher in both treatment groups for subjects with moderate renal impairment compared with those with mild impairment or normal renal function. However, the RR between the treatment groups was lower (1.19) among subjects with moderate renal impairment compared with subjects with mild renal impairment (1.81) or normal renal function (1.91).

4.8.4 Analysis of All-Cause Mortality

The CARES study also showed an increase in all-cause mortality on febuxostat, due primarily to the increase in CV death. A total of 442 deaths occurred in the study, with a higher number of deaths observed in the febuxostat group compared with allopurinol (243 vs 199, respectively). As shown in Table 4.j, sensitivity analyses of subjects on-drug or on-drug plus 30 days after drug discontinuation showed higher rates of death on febuxostat, consistent with the mITT analysis.

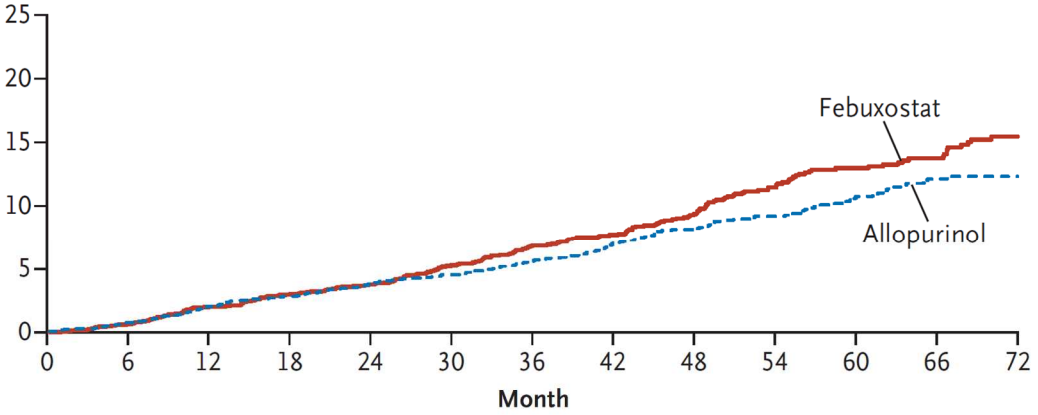
Table 4.j Summary of All-Cause Deaths (mITT)

	Subjects, n (%)		
	Febuxostat N = 3098	**Allopurinol N = 3092**	**Hazard Ratio [a] (95% CI)**
mITT	243 (7.8)	199 (6.4)	1.22 (1.01, 1.47)
On-drug	36 (1.2)	27 (0.9)	1.31 (0.80, 2.17)
On-drug plus 30 days	92 (3.0)	72 (2.3)	1.26 (0.93, 1.72)

mITT: modified intent-to-treat.
mITT analysis includes all deaths; on-drug plus 30 days includes all deaths occurring up to 30 days post-treatment; on-drug analysis includes only deaths occurring while receiving study drug.
[a] Febuxostat to allopurinol.

The time from randomization to the occurrence of all-cause mortality is presented as a Kaplan-Meier plot in Figure 4.f.

Figure 4.f Kaplan-Meier Plot of Time From Randomization to All-Cause Mortality



No. at Risk													
Febuxostat	3098	2828	2552	2179	1928	1666	1447	1251	1038	840	631	487	289
Allopurinol	3092	2812	2540	2161	1906	1648	1444	1215	1015	842	650	489	288

Source: White et al [9].

An analysis of all-cause mortality was performed with the vital status information obtained by OmniTrace (Table 4.k), which includes the incorporation of an additional 199 deaths (febuxostat n = 89, allopurinol n = 110). Given the high dropout rate observed in the study, the vital status information provided more complete data. These results did not show an increase in HR compared with the mITT. See Section 4.6 for details on vital status collection.

Table 4.k Summary of All-Cause Mortality Incorporating Vital Status (mITT)

	Subjects, n (%)		
	Febuxostat N = 3098	**Allopurinol N = 3092**	**Hazard Ratio [a] (95% CI)**
mITT	243 (7.8)	199 (6.4)	1.22 (1.01, 1.47)
mITT with vital status obtained by OmniTrace	332 (10.7)	309 (10.0)	1.09 (0.94, 1.28)

mITT: modified intent-to-treat.
[a] Febuxostat to allopurinol.

4.8.5 Exploratory Analyses to Understand the CV Death Data

In the CARES study, the rate of CV death was higher on febuxostat than allopurinol. In contrast, the other adjudicated components of the composite endpoint of nonfatal MI, and nonfatal stroke, and unstable angina with urgent coronary revascularization were similar between treatment groups. Several clinical assessments and exploratory analyses were performed to better understand and characterize the difference in CV death rate between febuxostat and allopurinol. Theses analyses included cause of death (Section 4.8.4), subgroups (Section 4.8.3), and sensitivity analysis based on time of occurrence of events (Section 4.8.3) and were discussed previously in the document.

Additional prespecified and post hoc analyses conducted included: clinical and laboratory assessments, relationship of CV death by final dose within renal function groups, relationship of CV death to sUA and flares and are discussed below. Overall, exploratory analyses of potential risk factors did not identify a plausible condition or circumstance to explain the difference observed for CV death.

Clinical and Laboratory Assessments

No differences between treatment groups were noted in changes from baseline in serum chemistries (calcium, sodium, potassium, magnesium), body weight, blood pressure and heart rate, or conduction intervals obtained by electrocardiograms (ECGs) during the study. In addition, all baseline parameters were similar between treatment groups

Relationship of CV Death Based on Final Dose Within Renal Function Groups

To evaluate the effect of renal function on CV death, a subgroup analysis of CV death was conducted and showed that there was no significant association between renal impairment and the difference in rates of CV death between febuxostat and allopurinol (Table 4.l). In subjects with moderate renal impairment, who would be expected to have a higher risk for CV events, the difference in CV death between the treatment groups was much less pronounced.

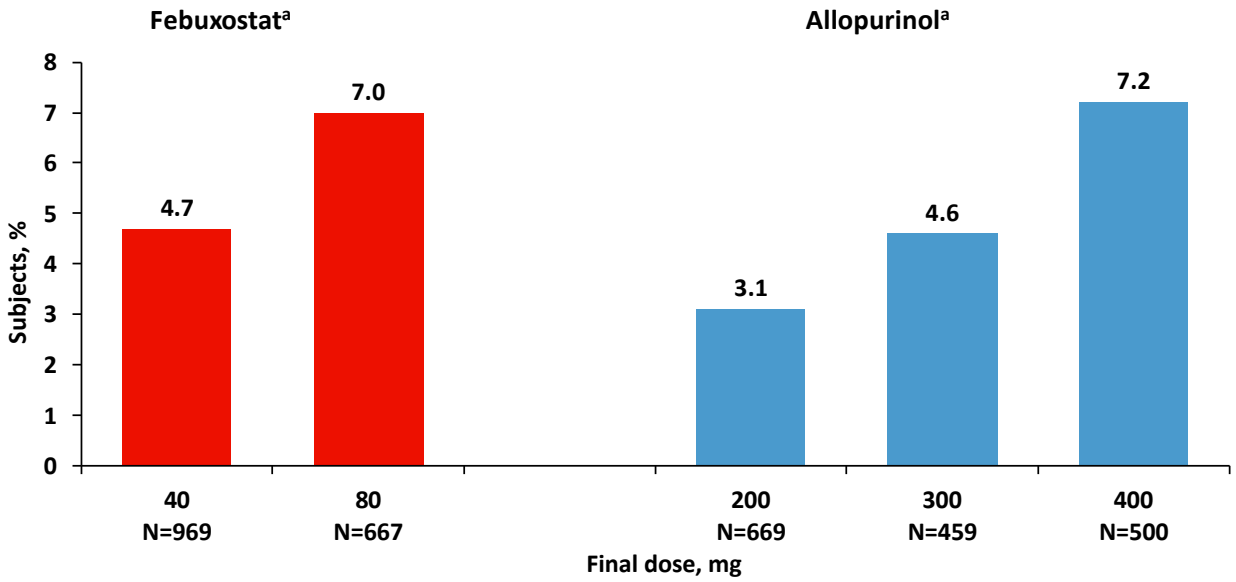
Table 4.l CV Deaths by Baseline Renal Function

Renal Function Strata	Subjects, n (%)		
	Febuxostat N = 3098	Allopurinol N = 3092	Hazard Ratio [a] (95% CI)
Normal/mildly impaired	41 (2.8)	21 (1.4)	1.87 (1.11, 3.17)
Moderately impaired	93 (5.7)	79 (4.9)	1.19 (0.88, 1.61)

CV: cardiovascular.
[a] Febuxostat to allopurinol.

As doses were titrated based on sUA response and not randomization, evaluation of the potential dose response is challenging in the CARES study. The effect of dose within the moderate renal function category on the rate of CV death, was summarized in an ad hoc analysis (Figure 4.g). This analysis showed that within the subgroup of subjects with moderate renal impairment (53% of the study cohort), the rate of CV death was higher in subjects who required dose titration to higher doses for both febuxostat and allopurinol. The ad hoc analysis of effect of dose within all renal function categories on the rate of CV death is summarized in Appendix 4.

Figure 4.g CV Death by Final Titrated Treatment Dose and Moderate Renal Impairment



CV: cardiovascular; sUA: serum uric acid.
[a] Febuxostat dose titrated based on sUA. Allopurinol dose titrated based on sUA and renal function. Of note, this is not a direct comparison of CV death rates between similarly efficacious doses of febuxostat and allopurinol.

To evaluate further the increases in CV death rates with the up-titration of doses, demographic and baseline characteristics, gout disease history, and CV history were summarized separately for subjects who required and did not require up-titration, both for all subjects and for the subset of subjects with moderate renal impairment. These analyses showed that subjects requiring up-titration (higher doses) had a greater gout and CV disease burden, particularly heart failure, than those not requiring up-titration. Thus, because of the study design in which doses are titrated to reach sUA <6.0 mg/dL, the higher percentage of CV death among subjects who required titration in both the febuxostat and allopurinol groups is likely due to the higher CV risk at baseline in these subjects. Characteristics for subjects with moderate renal impairment who required and did not require up-titration are shown in Table 4.m.

Table 4.m Characteristics of Subjects With Moderate Renal Impairment According to Dose Titration Requirements

Characteristic	Dose Increase		No Dose Increase	
	Febuxostat N = 667	Allopurinol N = 950	Febuxostat N = 969	Allopurinol N = 681
Age, years	66.9*	68.0*	69.5	70.1
≥65 years, n (%)	413 (61.9)*	632 (66.5)*	701 (72.3)	520 (76.4)
Serum urate, mg/dL	9.9*	9.5*	8.3	8.0
Tophus present, n (%)	149 (22.3)*	231 (24.3)*	202 (20.8)	127 (18.6)
>6 gout flares during year before randomization	81 (12.1)	124 (13.1)	93 (9.6)	80 (11.7)
History of MI	281 (42.1)	394 (41.5)	371 (38.3)	260 (38.2)
History of unstable angina	201 (30.1)	261 (27.5)	250 (25.8)	176 (25.8)
History of heart failure	220 (33.0)*	287 (30.2)*	186 (19.2)	137 (20.1)

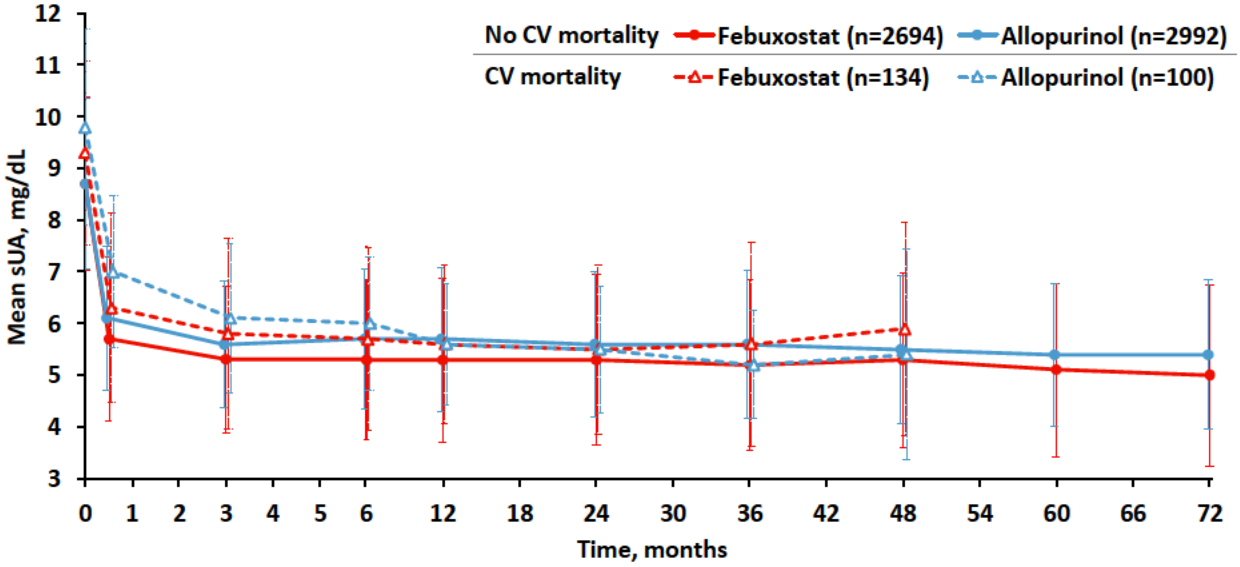
MI: myocardial infarction.
* P<0.05 for those requiring vs those not requiring a dose increase.

Relationship of CV Mortality and sUA or Gout Flare

An association between sUA levels and cardiorenal comorbid conditions has been reported [20-25,55,56]. Moreover, the inflammatory response associated with acute gout flares has been hypothesized to be potentially associated with CV events because of systemic inflammation. To explore the potential impact of sUA level and incidence of gout flares on CV death, the change from baseline in sUA and the incidence of gout flares per PY of exposure were assessed for those subjects with CV death (CV mortality) and the cohort of all CARES subjects excluding those who had CV death (no CV mortality). At baseline, sUA levels were higher in subjects with CV mortality versus subjects with no CV mortality (Figure 4.h). In the subjects with no CV mortality, febuxostat was also associated with lower sUA levels than allopurinol at most study visits. In the CV mortality cohort, sUA were not different for febuxostat vs allopurinol.

Overall in each treatment group, sUA levels were similar for subjects with CV mortality and for subjects with no CV mortality. Available evidence does not support a relationship between sUA levels and CV death.

Figure 4.h CV Mortality and Serum Urate Levels

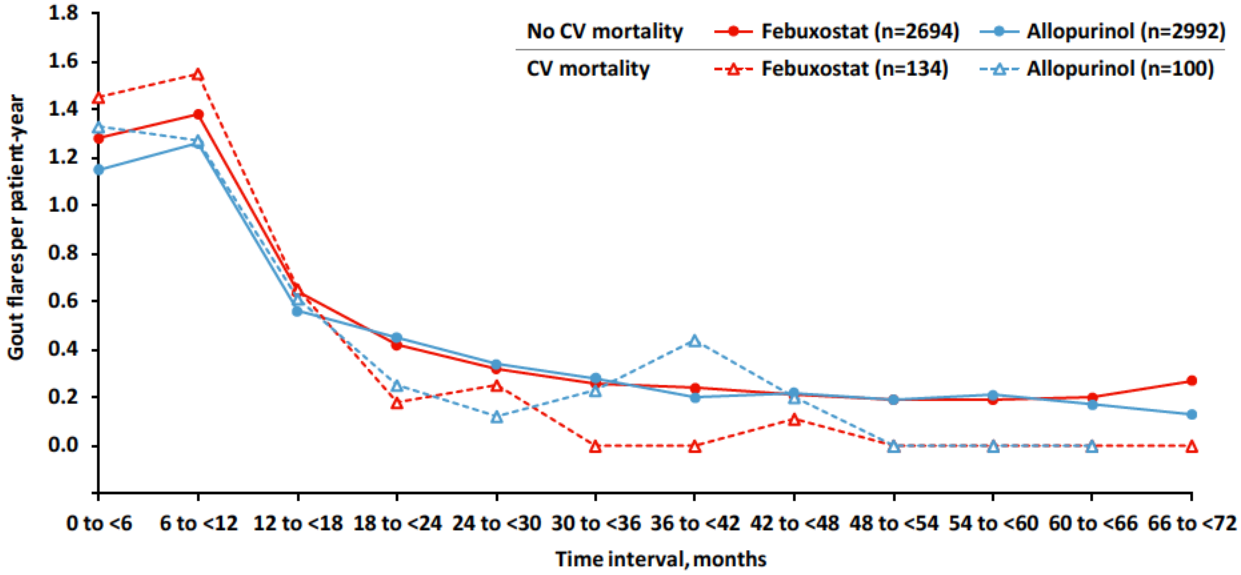


CV: cardiovascular, sUA: serum uric acid.
Baseline n for overall population were: no CV mortality subgroup febuxostat = 2964, allopurinol = 2992; CV mortality subgroup: febuxostat = 134, allopurinol = 100.

Gout flares requiring treatment in the first year in both treatment groups were slightly higher in subjects with CV mortality compared with subjects with no CV mortality, but generally lower for the remainder of the study period (Figure 4.i). Overall, gout flare rates were similar for febuxostat and allopurinol and decreased across the study period.

Available evidence, does not support a relationship between flare rates and CV death.

Figure 4.i CV Mortality and Gout Flares



CV: cardiovascular.
Baseline n for overall population were: no-CV mortality subgroup febuxostat = 2964, allopurinol = 2992; CV mortality subgroup: febuxostat = 134, allopurinol = 100.

4.8.6 Assessing the Impact of Subject Discontinuation

Despite efforts to retain subjects in the study as described in Section 4.6.4, there was a high rate of discontinuation from both study drug (57%) and study visits (45%). Higher rates of discontinuation of treatment can lead to concerns of missing a significant difference between treatment groups in the primary or secondary outcomes. Thus, there is potential that the missing data could impact the robustness of the study endpoints and create challenges to appropriate interpretation of the data. Multiple analyses were conducted to assess the potential impact of missing data including overall dropout rates, reason for dropout, timing of dropout, baseline characteristics of subjects who dropped out, and multiple imputation.

No differences between the 2 treatment groups were observed with regards to discontinuation rates, reason for discontinuation, and timing of the discontinuation. Further evaluation included whether pertinent baseline subject characteristics (eg, demographics, gout disease history, and CV history) were similar between subjects who discontinued from study visits compared with those who were completers. No differences in these characteristics were observed between subjects who discontinued study compared with subjects who completed the study.

These investigations support the assumption that subjects who were censored in the time-to-event analyses because of discontinuation from study drug or study visits were randomly distributed between the treatment groups. The baseline characteristics did not suggest a relationship between treatment and missing data due to premature discontinuation.

Events that occurred while subjects were no longer on randomized treatment could have potentially diluted the safety signal and biased the data toward the alternative hypotheses in the noninferiority design. Hence, the robustness of the primary endpoint results for the MACE composite and the secondary endpoints results for CV death were evaluated using a sensitivity analyses of events that occurred on-drug plus up to 30 days after last dose, since these events can be attributed more reliably to randomized treatment. In this sensitivity analysis, more than 80% of the subjects had complete data (ie, fewer subjects were censored for missing data in the time-to-event analyses). The results from this sensitivity analysis were consistent with the mITT analysis for both the primary endpoint and for CV death (Table 4.n).

Table 4.n Comparison of Sensitivity Analyses With mITT Analysis for MACE and CV Death

Analysis Set	Endpoint	Febuxostat N = 3098	Allopurinol N = 3092	HR (95% CI)
mITT	MACE composite	335 (10.8)	321 (10.4)	1.03 (0.87, 1.23) [a]
Sensitivity (on drug plus 30 days)	MACE composite	242 (7.8)	238 (7.7)	1.00 (0.82,1.22) [a]
mITT	CV death	134 (4.3)	100 (3.2)	1.34 (1.03, 1.73)
Sensitivity (on drug plus 30 days)	CV death	62 (2.0)	41 (1.3)	1.49 (1.01, 2.22)

CV: cardiovascular, MACE: major adverse cardiac event; mITT: modified intent-to-treat.
[a] 95% adjusted CI.

An additional sensitivity analysis used multiple imputation methodology to assign event outcomes to subjects who prematurely discontinued. Within the frame work of this analysis, the imputation process was repeated multiple times and repeated over a range of decreased to increased risk of events for febuxostat subjects after discontinuation. The risk for subjects on allopurinol was held constant. The results for the multiple imputation analyses were consistent with the results for the mITT analyses for the primary endpoint (Table 4.o) and for CV death.

Table 4.o Analysis of MACE Using Multiple Imputation

	Average Events After Imputation, n (%)			
Θ	Febuxostat	Allopurinol	HR (CI)	P-value [a]
0.8	459 (14.82)	471 (15.23)	0.970 (0.829, 1.134)	0.699
0.9	473 (15.27)	470 (15.20)	1.002 (0.861, 1.167)	0.975
1.0	488 (15.75)	472 (15.27)	1.033 (0.887, 1.203)	0.679
1.1	501 (16.17)	470 (15.20)	1.067 (0.915, 1.244)	0.409
1.2	514 (16.59)	470 (15.20)	1.097 (0.940, 1.279)	0.239

HR: hazard ratio; MACE: major adverse cardiac event.
Θ: Additional risk for an event after discontinuation among febuxostat subjects who discontinued; risk for allopurinol who discontinued was held constant. For example, Θ = 1.2 indicates a multiple imputation simulation in which febuxostat subjects who prematurely discontinued the study have an additional 20% risk of an event compared with febuxostat subjects that completed the study.
[a] P-value is for a test of treatment difference.

Further insight into the potential influence of missing data was obtained from the analysis of all-cause mortality incorporating the vital status information obtained by OmniTrace. The HR was lower (1.09; 95% CI 0.94, 1.28) in the analysis incorporating the vital status information compared with the HR in the mITT all-cause mortality analysis (1.22; 95% CI 1.01, 1.47). Hence, the results with more complete data did not show an increase in HR compared with the mITT analysis and the potential mortality risk on febuxostat was not diluted by the time to event analysis with censored (ie, missing data). See Section 4.6.5 for details on vital status collection.

Overall, these evaluations indicated that the missing data appeared to impact both treatment groups similarly and did not indicate that the missing data biased the results in favor of febuxostat. The results for the primary endpoint and for CV death in these sensitivity analyses were consistent to the overall mITT results.

4.9 Summary of Non-CV Safety

Overall, febuxostat and allopurinol exhibited similar safety profiles for adverse events and clinical laboratory test results in this study.

No noteworthy differences were observed between febuxostat and allopurinol in the incidences for the most frequent (≥5% in any treatment) treatment-emergent adverse events (TEAEs). An incidence difference of >1% between febuxostat and allopurinol treatment groups was observed for Preferred Terms (PTs) of arthralgia (8.5% vs 10.1%, respectively), hypertension (7.0% vs 8.7%, respectively), and urinary tract infection (5.1% vs 6.2%, respectively). When adjusted to event per 100 PY, a difference of ≥1 event per 100 PY between febuxostat and allopurinol, respectively, was observed for arthralgia (4.4 vs 5.4 events per 100 PY for febuxostat and allopurinol, respectively).

The study-drug related TEAEs reported in >0.5% of subjects in either the febuxostat or allopurinol group, respectively, were diarrhea (1.8% and 1.5%), nausea (0.7% and 0.5%), and rash (0.3% and 1.0%).

A total of 8.1% and 9.4% of subjects in the febuxostat and allopurinol groups, respectively, experienced a rash TEAE, using the rash Standardised MedDRA (Medical Dictionary for Regulatory Activities) Query (SMQ). In general, the incidences of rash PTs were higher in the allopurinol group than the febuxostat group. Similarly, rash events reported by the investigator to be related to treatment were higher in the allopurinol group (1.3%) than the febuxostat group (0.6%).

No apparent treatment-group differences were observed in the incidences of adverse events resulting in study drug discontinuation. The most notable treatment-related TEAE leading to study drug discontinuation was rash, which was higher in the allopurinol group (0.7%) than febuxostat group (0.2%). Several allopurinol subjects had rash serious adverse events leading to discontinuations of study drug, including 1 event of Stevens-Johnson syndrome.

No clinically meaningful differences were observed within or between the treatment groups for mean changes from baseline, shifts from baseline, or incidences of markedly abnormal results in serum chemistry tests. The percentages of subject in the febuxostat and allopurinol groups with alanine aminotransferase (ALT) ≥3 times the upper limit of normal (ULN) were 2.2% and 1.4%, respectively; aspartate aminotransferase (AST) ≥3 × ULN were 2.0% and 1.6%, respectively; and ALT and AST ≥3 × ULN concurrently were 1.0% and 0.8%, respectively. No clinically meaningful differences were observed within or between the treatment groups for mean changes from baseline, shifts from baseline, or incidences of markedly abnormal results in vital signs or ECG.

4.10 Strengths and Limitations of the CARES Study

CARES was the first CVOT of urate lowering drugs in subjects with gout and major CV or cerebrovascular disease. It was a large, double-blind, randomized study, that incorporated a predefined, comprehensive adjudication process for major CV endpoints to address the question of CV risk of febuxostat compared with allopurinol. It was long-term and adequately powered to obtain a sufficient number of relevant CV events to assess noninferiority in the MACE endpoint. Moreover, the study allowed for direct comparison of allopurinol and febuxostat using a treat-to-target dose-titration scheme.

Just like any study, there are inherent limitations in the study design and conduct. For example, although a comparison of study results for CV events could be made between febuxostat and allopurinol, the lack of a placebo arm precludes determination of either study drug's impact on CV risk compared with an untreated gout population. This is important since gout is associated with increased CV events and mortality (Section 3.2).

Additionally, because many subjects enrolled had previous exposure to allopurinol, there may be a potential bias for underestimation of adverse events with allopurinol as it would be expected that subjects who previously did not tolerate allopurinol would not have enrolled.

The CARES study was not designed for noninferiority for the individual MACE component endpoints. Furthermore, type 1 error control and noninferiority assessment were done solely for the primary endpoint and not the individual MACE components.

In this study, there were many subjects who discontinued from study drug and many subjects who did not complete follow-up. Higher rates of discontinuation of treatment can lead to concerns of missing a significant difference between treatment groups in the primary or secondary outcomes.

Analyses were conducted to assess the potential impact of missing data including overall dropout rates, reason for dropout, timing of dropout, baseline characteristics of subjects who dropped out, and multiple imputation. These additional analyses were consistent with the mITT analyses.

5.0 PRECLINICAL AND OTHER CLINICAL DATA RELEVANT TO CV SAFETY

Takeda reviewed the preclinical and other clinical data to investigate whether there was any mechanism of cardiac toxicity associated with febuxostat which might explain the higher rate of CV death with febuxostat observed in the CARES.

5.1 Preclinical Program

As a part of the standard drug development process, the potential for febuxostat to induce adverse CV changes was evaluated using in vitro and in vivo assessments.

The safety pharmacology studies (eg, hERG [human ether-à-go-go–related gene], purkinje fiber, [potassium rectifier channel] Na^{+}, Ca^{++} channels) demonstrated no abnormality associated with febuxostat that would lead to deleterious CV effects at therapeutic doses. Additionally, in animal models specific for CV disorders, febuxostat had no detrimental CV functional effects, but rather appeared to have beneficial CV effects [57-61].

5.2 Clinical Development Program

5.2.1 Phase 1 Study

In a thorough QT study in healthy volunteers at febuxostat doses of 80 and 300 mg QD for up to 4 days, no statistically significant changes were noted in QT interval with Fridericia correction method (QTcF) (Table 5.a) and QT interval with Bazett correction method (QTcB) interval from baseline in the febuxostat 80 or 300 mg QD regimens compared with placebo. The incidence of increases in QTcF and QTcB intervals from baseline of 30 to 60 msec was similar between febuxostat 80 and 300 mg QD, and placebo groups. No subject in any febuxostat treatment group experienced a >60 msec increase in QTcF or QTcB interval. These results showed there is no evidence that febuxostat will lead to prolongation of the QT interval.

Table 5.a Thorough QT Study of Febuxostat at Maximal Therapeutic and Supratherapeutic Doses in Healthy Volunteers

Comparison of Maximum QTcF Intervals							
	Mean of Maximum QTcF, msec				Difference Prom Placebo, msec		
	Placebo N = 41	Febuxostat 80 mg N = 41	Febuxostat 300 mg N = 41	Moxifloxacin 400 mg N = 41	Febuxostat 80 mg N = 41	Febuxostat 300 mg N = 41	Moxifloxacin 400 mg N = 41
Baseline	406.0	407.1	405.7	404.3	1.1	-0.3	-1.7
Day 1	396.5	398.6	398.5	406.8 *	2.1	2.0	10.3
Day 4	402.9	403.7	405.1	415.9 *	0.8	2.2	13.0

QT_CF: QT interval with Fridericia correction method.
* Statistically significant difference from placebo at the 0.001 level.

5.2.2 Phase 3 Development Program

In the initial 2 phase 3 studies (APEX and FACT), APTC events (CV death, nonfatal MI, nonfatal stroke) were numerically low, but there was an imbalance in the rate of events for febuxostat 80 and 120 mg compared with allopurinol or placebo (Table 5.b). Because of the small number of events in each study arm and the limited exposure on allopurinol in the long-term extension studies, there was uncertainty whether the findings represented an increased risk of CV events with febuxostat.

Table 5.b APTC Events in APEX and FACT

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

APTC: Antiplatelet Trialists' Collaborative; QC: once daily.
No events of nonfatal stroke were reported.
[a] CI are calculated based on binomial distribution.

As a result, Takeda conducted an additional phase 3 study (CONFIRMS) that assessed safety and efficacy of the febuxostat 40 and 80 mg doses compared with allopurinol in subjects with hyperuricemia and gout.

As shown in Table 5.c, examination of CV events in CONFIRMS did not show a higher rate of CV thromboembolic events with febuxostat than with allopurinol. The overall mortality rate and CV mortality rate were not increased. This study did not confirm the previous observation of a higher rate of CV events with febuxostat than with allopurinol.

Table 5.c Adjudicated APTC Events in CONFIRMS

	Subjects, n (%) 95% CI		
	Febuxostat 40 mg N = 757	**Febuxostat 80 mg N = 756**	**Allopurinol [a] N = 756**
All APTC events	0 0.00, 0.49	3 (0.40) 0.08, 1.16	3 (0.40) 0.08, 1.16
CV death	0 0.00, 0.49	0 0.00, 0.49	2 (0.26) 0.03, 0.95
Nonfatal MI	0 0.00, 0.49	1 (0.13) <0.01, 0.74	1 (0.13) <0.01, 0.74
Nonfatal stroke	0 0.00, 0.49	2 (0.26) 0.03, 0.95	0 0.00, 0.49

APTC: Antiplatelet Trialists' Collaborative; CV: cardiovascular; MI: myocardial infarction.
[a] Allopurinol dose (300 or 200 mg) based on renal function. N = 145 for 200 mg (estimated creatine clearance 30 to 59 mL/min).

A pooled analysis that included all 3 randomized phase 3 studies (APEX, FACT, and CONFIRMS) revealed a numerical imbalance in the number of CV thromboembolic events in the composite of CV deaths, nonfatal MI, and nonfatal strokes in subjects treated with febuxostat compared with allopurinol as shown in Table 5.d.

Table 5.d Adjudicated Major CV Events Pooled Analysis of Phase 3 Randomized Controlled Studies (APEX, FACT, CONFIRMS)

	Events, n (Rate per 100 Subject Years) 95% CI	
	Febuxostat N = 2690	**Allopurinol N = 1277**
All APTC events	10 (0.74) 0.36, 1.37	4 (0.60) 0.16, 1.53
CV death	3 (0.22) 0.05, 0.65	2 (0.30) 0.04, 1.08
Nonfatal MI	5 (0.37) 0.12, 0.87	2 (0.30) 0.04, 1.08
Nonfatal stroke	2 (0.15) 0.02, 054	0 0.00, 0.55

APTC: Antiplatelet Trialists' Collaborative; CV: cardiovascular; MI: myocardial infarction.
Adjudication was done prospectively in CONFIRMS and retrospectively in APEX and FACT.

5.3 Other CV Safety Study: FAST

Further understanding of the CV profile for febuxostat and allopurinol may be gained from an on-going CV safety study being conducted in Europe as a postauthorization requirement by Menarini (a partner of Teijin Pharmaceutical Companies, Takeda's alliance partner) the Febuxostat versus Allopurinol Streamlined Trial (FAST) [10]. FAST is a PROBE study

comparing febuxostat to allopurinol conducted in the clinical setting (general practitioners and specialists). The enrollment criteria included subjects aged >60 years, use of allopurinol within the last 6 months, and 1 additional CV risk factor. Approximately 6100 subjects have been enrolled.

The primary endpoint is the first occurrence of the composite of CV death, nonfatal MI, or nonfatal stroke. The primary analysis is a noninferiority analysis with a noninferiority upper limit for the HR for the primary outcome of 1.3. A total of 456 primary events are required to show noninferiority between the febuxostat and allopurinol treatment arms.

Before randomization, all subjects received dose-optimized allopurinol according to clinical judgement with a goal to achieve either a sUA level of <6 mg/dL or the maximum tolerated dose for that subject. Following dose optimization period, subjects underwent a washout period of 1 week after randomization and before initiating study treatment.

Subjects randomized to allopurinol received allopurinol at the dose determined before randomization. Allopurinol dosing may be in the range of 100 to 900 mg per day. Subjects randomized to febuxostat received 80 mg initially, which could have been increased to 120 mg QD at the discretion of the investigator. During the study, the dose of both treatments can be adjusted according to clinical judgement.

Subjects are followed-up for an average of 3 years from randomization. Endpoint data are adjudicated by an independent endpoint committee blinded to randomized treatment. A steering committee is monitoring the conduct of the study, and a data safety monitoring board is reviewing the unblinded data with the authority to recommend changes to study conduct.

Like CARES, FAST is a long-term, adequately powered study, with adjudication of CV events to assess if febuxostat was noninferior to allopurinol in the APTC endpoint of CV death, nonfatal MI, or nonfatal stroke.

Unlike CARES, FAST inclusion criteria allow for enrollment of a subject population with a lower CV risk profile. In addition, FAST used a starting dose of febuxostat 80 mg QD with titration to 120 mg; these doses are higher than the dosing recommendations in the US (febuxostat 40 to 80 mg QD). The PROBE design allows the real-world use of the 2 drugs to be compared, and allows for dose adjustments during the study, if required. FAST enrolled all subjects into an allopurinol dose-optimization and washout period before randomization into open-label treatment. The follow-up of outcomes is done by record-linkage to hospitalizations and deaths and by direct reporting by study site coordinators or other delegated study staff, which may provide efficiency in data management.

The recruitment in FAST ended in January 2018 and the clinical study report is expected by August 2020.

6.0 POSTMARKETING SURVEILLANCE

The Takeda global safety database provides safety data information of febuxostat, with an estimated global exposure of 15.1 million PY since first approval (IBD of 21 April 2008). As of October 2018, the total estimated US exposure is 1.4 million PY.

Takeda uses the Oracle Health Sciences Empirica Signal tool to assist in identifying potential safety signals via disproportionality analyses. Empirica detects and quantifies safety signals by using advanced data mining techniques that can be applied to events or combination of events in a safety database. Signal strength is derived by evaluating all the possible drug event combinations occurring in adverse event reports and identifying suspect drug-event pairs. Disproportionality analysis was performed for CV events and febuxostat on cases contained in the FDA Adverse Event Reporting System (FAERS – 2018Q2) and the World Health Organization's global Individual Case Safety Report Database (VigiBase 2018Q3). This analysis of drug-event combinations for CV events failed to reach a threshold that would generate a hypothesis of a potential signal.

As of 29 October 2018, a search of the Takeda Global Safety Database was conducted for CV events using criteria for MACE outlined in the CARES CEC Charter. This investigation revealed 2004 adjudicated and nonadjudicated CV events; of these, a total of 1504 events occurred in clinical studies. The other 500 CV events were captured solely from spontaneously reported sources and were received over a 10-year exposure period. No CV signal was identified on the basis of the review of these spontaneously reported cases.

As of 07 November 2018, a search of the Takeda Global Safety Database was conducted to identify all spontaneously reported fatal cases associated with febuxostat use. A case series was obtained using the broad cardiac SMQs (arrhythmia related investigations, signs and symptoms, cardiac arrhythmias, cardiac failure, cardiomyopathy, ischaemic heart disease, Torsade de pointes/QT prolongation, Torsade de pointes, shock-associated conditions, and shock-associated circulatory or cardiac conditions excluding Torsade de pointes), which were applied to identify fatal CV events. The narrow SMQ embolic and thrombotic events was also used. The search returned a total of 130 cases from postmarketing sources, of which 72 were spontaneous reports, 41 were from postmarketing studies (PMS) with an investigator protocol; the remaining 17 from other PMS sources. These numbers are small in contrast with the 134 adjudicated cases of CV death reported in the CARES study in subjects treated with febuxostat.

Postmarketing data are limited because there are no comparable populations of individuals for a comparison and there is underreporting of events. The number of postmarketing fatal CV events from spontaneous reporting are small when compared with CV deaths that occurred in the context of clinical studies. The postmarketing data have been reviewed as part of Takeda's ongoing surveillance of potential safety signals. No signal for CV events or CV death with febuxostat has been observed through pharmacovigilance activities, including signal detection activities. Further, this review did not provide any additional information which could help further inform the higher rate of CV death with febuxostat observed in the CARES study.

7.0 LITERATURE REVIEW

Takeda conducted a search of the scientific and medical literature for any relevant studies conducted that evaluated the CV risk (MACE) of febuxostat, which could provide further insight into the cardiac safety profile of febuxostat and put the CARES study findings into context. These studies are summarized below.

- A population-based cohort study by Zhang et al, in 99,744 patients with gout, aged ≥65 years, and who initiated XOIs febuxostat or allopurinol was conducted using claims data from US Medicare (2008 to 2013) to evaluate CV risk in older patients [62]. All patients were continuously enrolled in Medicare parts A/B/D for ≥1 year and free of a given drug prior to the first dispensing date (index date). The primary outcome was a composite CV endpoint of MI or stroke. Secondary outcomes were comprised of MI, stroke, coronary revascularization, and new and recurrent heart failure requiring hospitalization. All-cause mortality was captured, but causes of death were not possible to determine. The HR for the primary outcome was 1.01 (95% CI 0.94, 1.08) when comparing febuxostat with allopurinol. The secondary outcomes of MI, stroke, coronary revascularization, and all-cause mortality were 1.03 (95% CI 0.94, 1.13), 0.98 (95% CI 0.87, 1.10), 0.95 (0.87, 1.03), and 0.95 (95% CI 0.89, 1.02), respectively, and showed no differences between febuxostat and allopurinol. A trend toward an increased, but not statistically significant, risk for all-cause mortality was noted in patients who used febuxostat for over 3 years versus allopurinol for over 3 years. Furthermore, a relevant subgroup analysis that included patients with high CV risk and defined similar to the CARES's study inclusion criteria, showed no significant differences in the primary and secondary outcomes between the febuxostat and allopurinol groups. The authors concluded that the discrepancy in results for mortality between CARES study and this study may be due to the differences in the underlying populations. The CARES study enrolled patients with high CV risk, defined as a history of major CV or cerebrovascular disease including MI, hospitalized unstable angina, coronary or cerebrovascular revascularization procedure, stroke, hospitalized TIA, peripheral vascular disease or diabetes mellitus with micro/macrovascular complications. However, this study included both patients with and without CV disease. The key limitations of this study were that the Medicare claims data did not provide information on cause-specific mortality, family history of CV disease, and severity of gout, which could have led to residual confounding. The mean follow-up time was around 1.2 years, which led to less precise estimates for the long-term effects of febuxostat on CV risk as well as all-cause mortality although the study still included many patients (n = 23,317) with more than 2 years of follow-up.
- Febuxostat for Cerebral and CaRdiorenovascular Events PrEvEntion StuDy (FREED) was a multicenter Japanese, prospective, randomized, open-label, blinded endpoint study, which enrolled 1070 elderly subjects with hyperuricemia who were at risk for cardiorenal events [63]. Subjects were randomly assigned to receive oral febuxostat or conventional therapy for 36 months which could be allopurinol or no uric acid-lowering treatment. In the febuxostat group, the dose was increased stepwise from 10 to 40 mg per day if tolerated. In the non-febuxostat group, allopurinol 100 mg was considered if sUA was elevated. A total of 537 subjects received febuxostat and the average dose at the end of the study was 29 mg/day. Of

the 533 subjects in the nonfebuxostat group, 27% received allopurinol 100 mg. The primary composite endpoint comprised of cerebral or cardiorenal vascular disease death, new or recurring cerebrovascular disease, new or recurring nonfatal coronary artery disease, cardiac failure requiring hospitalization, arteriosclerotic disease requiring treatment, renal impairment, new atrial fibrillation, or death due to other causes. Febuxostat significantly reduced the rate of the primary endpoint, with an HR of 0.75 (95% CI 0.59, 0.95, p = 0.017). For the endpoint composite of death from any cause or nonfatal cerebrovascular or coronary events, there was not a significant difference between the 2 groups. The key differences of this study in comparison to CARES were that it was not conducted in subjects with gout and studied lower doses of febuxostat and allopurinol.

- A retrospective cohort study conducted by Takeda Health Economics and Outcomes Research called the "Major Cardiovascular Events in Gout Patients with Cardiovascular Disease or Heart Failure and Chronic Kidney Disease Initiating on Allopurinol or Febuxostat (Uloric)" examined the impact of an individual XOI agent on MACE, including MI, stroke, TIA, nontraumatic LE amputation or coronary, cerebrovascular or LE revascularization [64]. The data sources for this retrospective cohort study were the Truven Marketscan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits Amount databases. The study included 2426 in-patients with moderate to severe CKD and CV disease/heart failure treated with either allopurinol or febuxostat (January 2009 to June 2013) and who were followed during treatment until withdrawal, discontinuation of the qualifying ULT, or use of the alternate study agent. A total of 162 MACE occurred during follow-up in 3.8% and 7.2% of febuxostat and allopurinol cohorts respectively. The MACE rate per 1000 PY (95% CI) in the febuxostat cohort was 51.8 (28, 87) as compared with the allopurinol cohort, which was 99.3 (84, 117). In this study patients with moderate to severe CKD and CV disease /heart failure initiating on febuxostat had a significantly lower rate of MACE than patients initiating on allopurinol. It was mentioned that these results may be due to the direct effects of lower sUA or the effect of reduced oxidative stress and other pleiotropic effects on the endothelium. Additionally, they noted it is unclear if this is due to channeling, greater clinical effectiveness on the part of febuxostat or to allopurinol under-dosing in patients with renal impairment.
- In a small inception cohort study in Spain, the risk of new CV events with XOI was assessed in 213 and 43 confirmed patients with gout who had initiated treatment with allopurinol and febuxostat, respectively, and who had at least 6 months of follow-up [65]. The primary outcome was new CV events (CV death, CHD, CHF, stroke, peripheral artery disease) after XOI initiation. Of note, this study is limited by a small sample size and short follow-up duration of median 9.5 months. Among patients with gout and prior CV disease, febuxostat was associated with significant increased risk of new CV events compared with allopurinol, but no significant difference between allopurinol and febuxostat was observed among patients without prior CV disease. The topline data were presented during a late-breaking abstract poster session at the 2018 ACR/Association of Rheumatology Health Professionals Annual Meeting but additional details on this study have yet to be published.

Overall, published studies have varied results and do not support an increased CV risk with febuxostat.

8.0 ASSESSMENT OF CV SAFETY OF FEBUXOSTAT

In assessing the overall CV safety of febuxostat, Takeda has carefully considered results from the CARES study, as well as the totality of available evidence, including data from the registration studies, postmarketing safety signal assessment, and literature.

8.1 CARES

The CARES study demonstrated noninferiority of febuxostat to allopurinol for the primary endpoint of MACE in subjects with gout and major CV or cerebrovascular disease. The rate of CV death was higher on febuxostat than allopurinol; however, there is a lack of concordance in the results for CV death and adjudicated nonfatal CV events, including MI, unstable angina with urgent coronary revascularization, arrhythmias, and hospitalization for heart failure. With a difference in CV death, it would be clinically expected that 1 or more of the nonfatal CV events would also be different. All-cause mortality was also higher with febuxostat than allopurinol largely because of these differences in CV death.

Changes from baseline in blood pressure and in serum electrolytes were not different across the treatment groups. There were also no clinically relevant ECG abnormalities observed. In subjects with moderate renal impairment who would be expected to have a higher risk for CV events, the difference in CV death between the treatment groups was much less pronounced. Several clinical assessments and exploratory analyses were performed to better understand and characterize the difference in CV death rate observed between febuxostat and allopurinol. These analyses included cause of death, subgroups, and sensitivity analysis based on time of occurrence of events. Additional prespecified and post hoc analyses included clinical and laboratory assessments, relationship of CV death by final dose within renal function groups, relationship of CV death to sUA and flares. Overall, these exploratory analyses of potential risk factors did not identify a plausible condition or circumstance to explain the difference observed.

An important limitation of the CARES study is the high discontinuation rate and loss to follow-up. As with any treatment for gout, the resilience of subjects to sustained treatment over years is challenging for patients with gout as seen in the phase 3 studies. High rates of treatment discontinuation can lead to concerns of missing a significant difference between treatment groups in the primary or secondary outcomes. Multiple analyses were conducted to assess the potential impact of missing data, including overall dropout rates, reason for dropout, timing of dropout, baseline characteristics of subjects who dropped out, and multiple imputation. The conclusions from these analyses were consistent with the overall results.

Approximately equal numbers of subjects discontinued follow-up in the 2 treatment groups, and the baseline characteristics of these participants were similar to those subjects who completed follow-up. Efforts were made to obtain final vital status on all subjects who were lost to follow-up or early terminated from the study excluding those known to have died. Vital status was obtained for 87% of subjects in the study. These additional data allowed further examination into all-cause mortality analyses for study subjects. This analysis showed a reduction in the HR compared with the mITT analysis, and most importantly, did not show an increase.

Given the results for CARES, Takeda thoroughly evaluated all available sources of data to assess CV safety for febuxostat.

8.2 Development Program

In the phase 3 APEX and FACT studies, APTC events (CV death, nonfatal MI, nonfatal stroke) were numerically low, but there was an imbalance in the rate of events for febuxostat 80 and 120 mg compared with allopurinol or placebo. For both APEX and FACT, the APTC adjudication was done retrospectively as part of a safety review after the studies were completed.

To address this issue, the CONFIRMS study was conducted with prospective adjudication of APTC events. In CONFIRMS, no APTC events were observed in the febuxostat 40 mg group, and the febuxostat 80 mg and allopurinol groups had the same rate of APTC events (0.4%). No deaths were observed with febuxostat and 2 deaths (0.3%) with allopurinol.

In the pooled analysis that included all the 3 randomized-controlled studies (APEX, FACT, and CONFIRMS), the CV events and deaths were adjudicated to 1 of the predefined endpoints from the APTC composite of CV deaths, nonfatal MI, and nonfatal strokes. Although the number of APTC events was small, a higher number was observed in febuxostat 80 and 120 mg than in subjects treated with allopurinol. For the combined febuxostat-treated subjects, the rate of APTC events was low. There were too few individual APTC events to draw meaningful comparisons. However, there were 3 deaths (0.11%) for all febuxostat-treated subjects combined and 2 deaths (0.16%) for the allopurinol treatment group.

8.3 Other Relevant Evidence

There was no signal for increased CV risk for febuxostat from nonclinical data or from a QTc study conducted in healthy subjects. Postmarketing signal detection also revealed no signal for CV events or CV death with febuxostat. Published studies in the literature have varied results and do not support an increased CV risk with febuxostat.

8.4 Overall CV Safety Summary

Following comprehensive clinical assessments and exploratory analyses, Takeda has been unable to determine any contributing factors or identify a population at risk for a higher rate of CV death in the CARES study. When accounting for the totality of the evidence, which includes the lack of concordance between the individual MACE components, the inability to explain the finding, and the absence of biological plausibility, there remains uncertainty about the reliability of the observation. However, as described in Section 10.4.2 (Risk Management), the seriousness of the observation makes it important that these findings are fully communicated to prescribers and patients for consideration in treatment decisions.

While the CARES study was conducted in a high-risk CV population, the ongoing FAST study will add to the understanding of the CV profile for febuxostat and allopurinol in a broader gout population. The recruitment in FAST ended in January 2018 and the clinical study report is expected by August 2020.

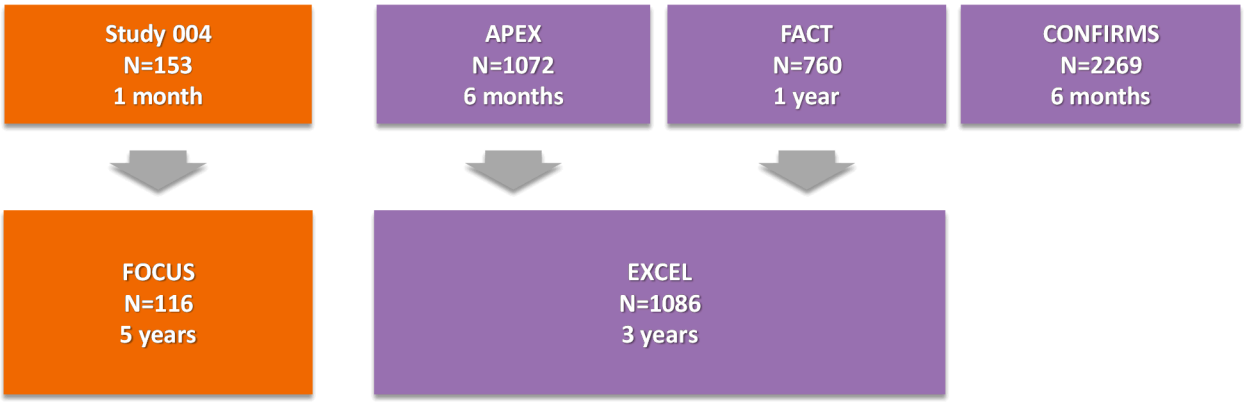
9.0 FEBUXOSTAT EFFICACY

On the basis of clinical and scientific evidence [6,39], it has been well established that treating to sUA target is the best approach for treating gout and, therefore, serum urate reduction is the gold standard endpoint for efficacy studies in gout. FDA considers it acceptable for use as a primary efficacy clinical study endpoint for drug approval (fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm613636, Surrogate Endpoints That Were the Basis of Drug Approval or Licensure, Accessed 03 December 2018). Therefore, the primary endpoint for pivotal phase 3 studies was the proportion of subjects achieving a target sUA less than 6 mg/dL, and the entry criteria required that subjects have a sUA ≥8 mg/dL.

9.1 Clinical Efficacy in the Febuxostat Development Program

The primary efficacy endpoint in the development program was the proportion of subjects achieving a target sUA of ≤6 mg/dL. Efficacy of febuxostat was supported by the results of 6 key studies (Figure 9.a) that enrolled a total of 4254 subjects with hyperuricemia and gout, with baseline sUA ≥8.0 mg/dL [29-32,66,67].

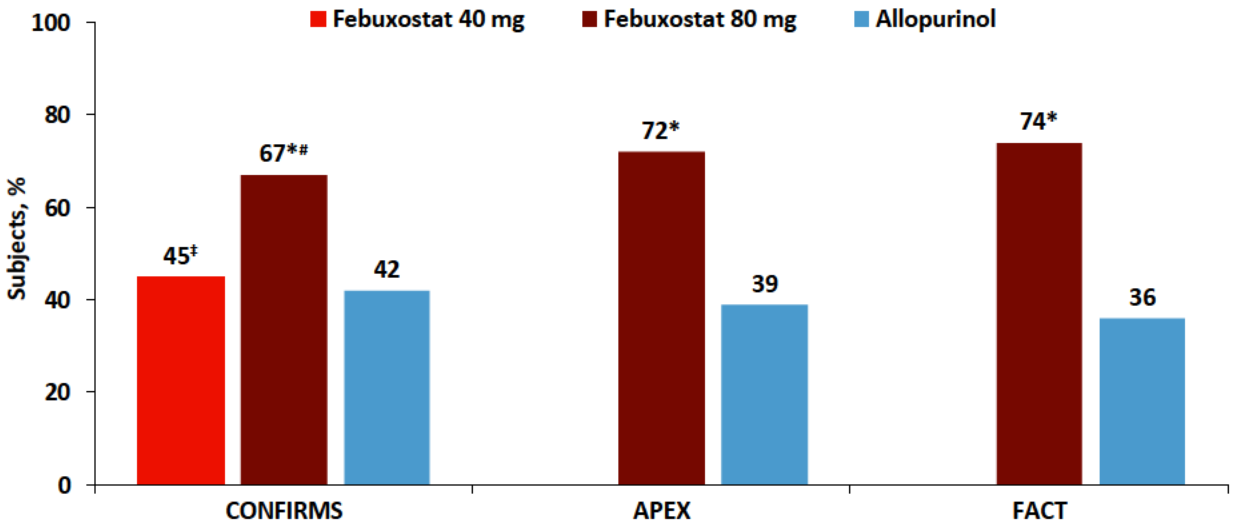
Figure 9.a Febuxostat Clinical Development Program Supporting Approval



Study 004, APEX, FACT, and CONFIRMS were randomized, double-blind studies. FOCUS and EXCEL were open-label extension studies.

The febuxostat phase 3 randomized clinical studies (APEX, FACT, and CONFIRMS) demonstrated that febuxostat 40 and 80 mg were efficacious in achieving and maintaining the target sUA level of <6.0 mg/dL (Figure 9.b). The urate lowering efficacy of febuxostat 80 mg QD was statistically significantly higher compared with allopurinol 300 mg (APEX, FACT, and CONFIRMS).

Figure 9.b Subjects Achieving sUA <6 mg/dL at Final Visit in APEX, FACT, and CONFIRMS

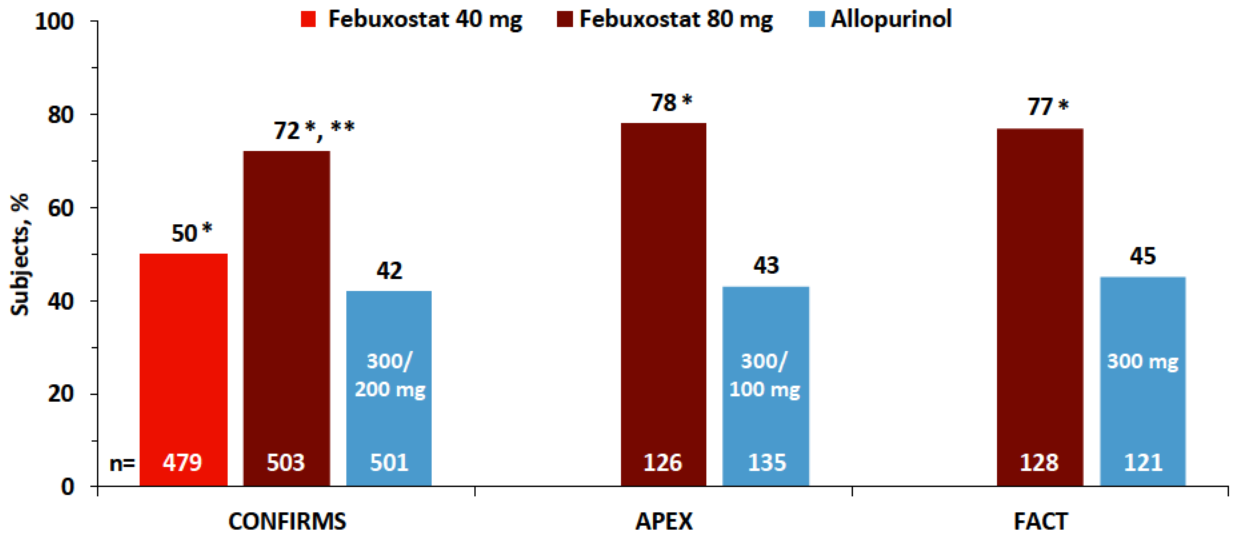


sUA: serum uric acid.
* P<0.001 vs allopurinol.
# P<0.001 vs febuxostat 40 mg.
‡ Noninferior to allopurinol.

These studies confirmed the durable and dose-dependent urate-lowering efficacy of febuxostat 40 and 80 mg QD compared with placebo (APEX) and the active comparator, allopurinol.

In the CONFIRMS study, the urate-lowering efficacies of febuxostat 40 and 80 mg were statistically significantly higher than allopurinol in subjects with mild to moderate renal impairment (eCrCl >30 to 89 mL/min) (Figure 9.c) [32].

Figure 9.c Subjects With Renal Impairment Achieving sUA <6 mg/dL at Final Visit in APEX, FACT, and CONFIRMS



sUA: serum uric acid.
Renal impairment defined as eCrCl >30 to 89 mL/min.
* P<0.05 vs allopurinol; ** P<0.05 vs febuxostat 40 mg.

The consistent benefit of febuxostat 80 mg compared with commonly used doses of allopurinol was observed in subjects with more severe gout as reflected by very high levels of sUA (≥10 mg/dL) and tophi.

In subjects with baseline sUA levels of ≥10.0 mg/dL in CONFIRMS, the proportion of subjects with a final visit sUA level of <6.0 mg/dL was 49% in the febuxostat 80 mg QD group compared with 27% in the febuxostat 40 mg QD and 31% in the allopurinol groups.

In APEX and FACT, the percentages of subjects whose sUA levels were <6.0 mg/dL at the final visit in subjects with baseline sUA levels of ≥10.0 mg/dL were 64% in the febuxostat 80 mg QD, 67% in the febuxostat 120 mg QD, and 21% in the allopurinol groups, respectively.

In subjects with tophi in CONFIRMS, the proportion of subjects with a final visit sUA <6.0 mg/dL was 57% in the febuxostat 80 mg QD group compared with 35% in the febuxostat 40 mg QD and 32% in the allopurinol groups. In subjects with tophi in APEX and FACT, a similar pattern was observed between febuxostat and allopurinol dose groups.

The persistence of efficacy was further demonstrated by data from the long-term, open-label extension studies (EXCEL and FOCUS) in which the long-term maintenance of sUA <6.0 mg/dL was observed with up to 5.5 years of febuxostat treatment [66,67]. Following persistent long-term urate lowering, the proportion of subjects with flares also continued to decline, achieving close to zero flare rates by 3 to 5 years, depending on the study duration. For subjects who had a tophus at baseline, sustained sUA level reductions of <6.0 mg/dL showed a benefit in the reduction in size of the primary palpable tophus.

In the EXCEL extension study, the efficacy of febuxostat was also evaluated in subjects who failed to achieve target sUA on open-label randomized treatment with allopurinol and who were subsequently treated with open-label febuxostat. Most of these subjects received 80 mg febuxostat. Although this was not a randomized comparison, the majority (67%) of the subjects who received febuxostat second line after an inadequate response to allopurinol achieved a target sUA <6 mg/dL. Conversely, a very small proportion (9%) who switched to allopurinol from febuxostat achieved <6 mg/dL.

9.2 Clinical Efficacy in CARES

CARES was a CV safety study and was not designed to assess efficacy; however, efficacy parameters, such as sUA level, gout flares, and presence of tophus were collected and summarized as post hoc exploratory endpoints. There were key differences in the designs between the CARES study and pivotal phase 3 studies that were relevant to urate lowering efficacy assessment. In the CARES study, the entry criteria required a sUA ≥7 mg/dL or a sUA ≥6 mg/dL with frequent flares or the presence of tophi (Appendix 1). These criteria allowed enrollment of subjects with lower baseline sUA than in the pivotal phase 3 studies, which enrolled subjects with sUA ≥8 mg/dL. Moreover, doses of febuxostat and allopurinol were up-titrated to achieve target sUA of <6 mg/dL. These key study design differences in combination could contribute to smaller differences in proportion of subjects achieving <6 mg/dL treatment target between treatment arms in CARES.

In CARES, better sUA reduction (ie, <6.0 and <5.0 mg/dL) was achieved with febuxostat compared with allopurinol at titrated doses, while demonstrating similar flare rates over the duration of the study. This provides additional evidence beyond what was demonstrated in the febuxostat clinical development program, where better urate lowering was achieved with febuxostat compared with allopurinol fixed at commonly used doses.

9.2.1 sUA

The proportion of subjects achieving sUA <6.0 mg/dL was higher on febuxostat than allopurinol at Week 2, and thereafter a small but consistently higher rate was maintained up to 60 months. Additionally, for the sUA target <5.0 mg/dL, a much higher percentage of subjects in the febuxostat arm achieved the target at each visit up to Month 72 compared with allopurinol. The proportion of subjects with sUA <6.0 mg/dL and <5.0 mg/dL is summarized by treatment group and visit in Table 9.a.

Table 9.a Proportion of Subjects With Serum Urate Levels <6.0 mg/dL and <5.0 mg/dL by Visit

	sUA <6.0 mg/dL		sUA <5.0 mg/dL	
Visit	Febuxostat (N = 3098) % (n/N)	Allopurinol (N = 3092) % (n/N)	Febuxostat (N = 3098) % (n/N)	Allopurinol (N = 3092) % (n/N)
Week 2	60.8 (1757/2892)	50.2 (1456/2899)	33.8 (978/2892)	18.9 (549/2899)
Month 3	73.1 (1975/2701)	69.4 (1863/2686)	42.8 (1156/2701)	26.7 (716/2686)
Month 6	71.9 (1823/2537)	66.4 (1680/2530)	43.9 (1113/2537)	28.3 (717/2530)
Month 12	72.5 (1544/2131)	66.1 (1423/2152)	46.0 (980/2131)	30.8 (662/2152)
Month 18	72.2 (1282/1775)	68.0 (1194/1757)	47.3 (839/1775)	32.5 (571/1757)
Month 24	73.4 (1159/1580)	67.6 (1052/1557)	46.1 (728/1580)	32.0 (498/1557)
Month 36	73.3 (836/1140)	69.5 (776/1117)	49.6 (566/1140)	33.8 (378/1117)
Month 48	72.0 (575/799)	72.5 (567/782)	48.9 (391/799)	37.9 (296/782)
Month 60	75.7 (387/511)	71.8 (359/500)	54.2 (277/511)	40.0 (200/500)
Month 72	74.5 (199/267)	75.0 (186/248)	57.7 (154/267)	44.0 (109/248)

sUA: serum uric acid.

Additionally, regardless of baseline renal function, a higher percentage of febuxostat-treated subjects achieved the target of <5.0 mg/dL, while the degree of success achieving the <6.0 mg/dL target varied with renal function category. Notably, in subjects with moderate renal impairment, a higher percentage of febuxostat treated subjects achieved sUA target <6.0 mg/dL compared with allopurinol for the duration of the study, while in subjects with mild renal impairment a numerically higher percentage of subjects achieved the same target with febuxostat compared with allopurinol. In subjects with normal renal function, a higher percentage of subjects achieved the <6.0 mg/dL target consistently up to 24 months.

9.2.2 Gout Flare

The proportion of subjects with gout flares requiring treatment is summarized for febuxostat and allopurinol treatments groups in Table 9.b. The proportions of subjects with gout flares requiring treatment were marginally higher overall and within the first year of treatment in the febuxostat treatment group than the allopurinol group. Flare rates were similar between treatment groups after the first year of treatment.

Table 9.b Proportion of Subjects With Gout Flares Requiring Treatment

Interval	Febuxostat (N = 3098) % (n/N)	Allopurinol (N = 3092) % (n/N)
Overall	46.8 (1450/3098)	44.8 (1386/3092)
≤1 year	41.1 (1272/3098)	38.3 (1184/3092)
>1 year	26.8 (597/2229)	27.2 (608/2232)

A subject who reported >1 gout flare during the same time interval was counted only once for that time interval. All flares up to 30 days after a subject's final dose of study drug were included in the analyses.

The incidence of gout flares requiring treatment varied among the different renal function categories. In subjects with moderate renal impairment, the incidence was slightly higher overall and for the period ≤1 year with febuxostat compared with allopurinol, while the incidence was similar for the period >1 year. In subjects with mild renal impairment, the rates were generally similar overall and for both periods of ≤1 year and >1 year between febuxostat and allopurinol treatment arms. In contrast, in the normal renal function group, the flare rates were lower overall and at both ≤1 year and >1 year periods with febuxostat compared with allopurinol.

Flare rates were also summarized as rates per PY of exposure. Overall flare rates per PY were similar between the febuxostat and allopurinol treatment groups (0.68 per PY and 0.63 per PY, respectively). The flare rate per PY was marginally higher in the febuxostat group during the first year of treatment compared with the allopurinol group, but similar during the time intervals after the first year of treatment.

9.2.3 Tophi

Among subjects with tophi at baseline, the rates of tophus resolution were similar between the febuxostat and allopurinol treatment groups during all time intervals. To achieve cumulative tophus resolution rates greater than 50%, both treatment groups required at least 3 years of ULT treatment.

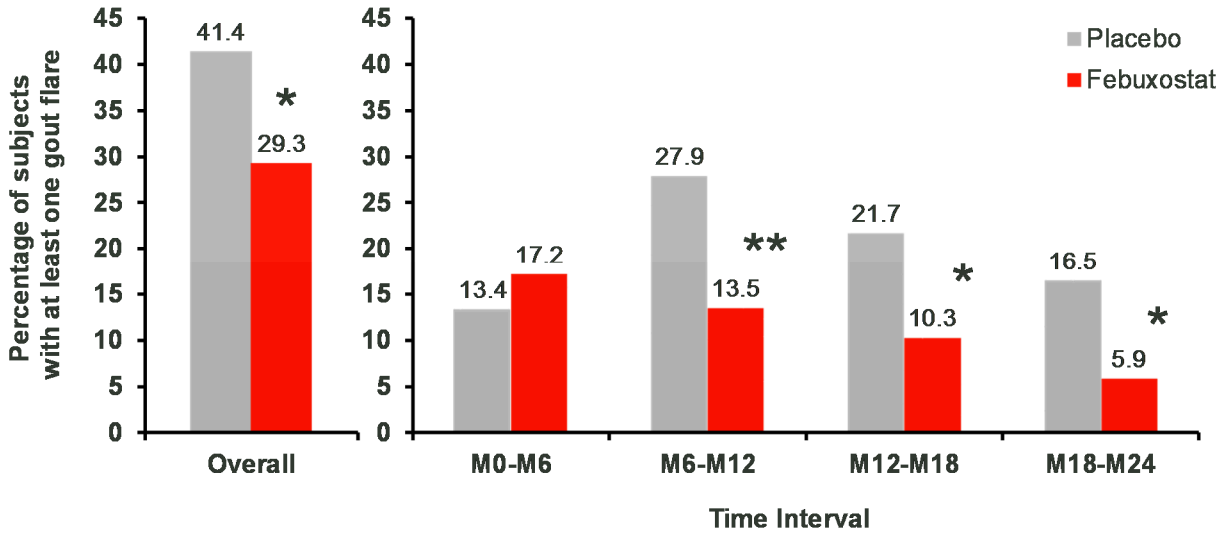
9.3 Additional Efficacy Data From a Febuxostat Clinical Study

Evidence for clinical benefits of ULT with febuxostat has come from a recent 2-year randomized control study comparing gout flares in patients with early gout [68]. Assessment of joint damage was also conducted with x-rays and magnetic resonance imaging (MRI). In this randomized, double-blind, placebo-controlled study, subjects with sUA ≥7.0 mg/dL and eGFR ≥60 mL/min were randomized to either febuxostat or placebo for up to 2 years.

Subjects received either daily febuxostat therapy titrated to serum urate <6 mg/dL or placebo. All subjects had early gout, defined as having experienced 2 or fewer gout flares in total and only 1 flare during the previous 12 months. All subjects also received gout flare prophylaxis for the first 6 months of the study; subjects who were either nonresponsive or intolerant to prophylaxis could be managed at the discretion of the investigator.

A total of 314 subjects received treatment with placebo (n = 157) or febuxostat (n = 157). During the first 6 months, the febuxostat group showed a slightly higher percentage of subjects with at least 1 flare, which was not statistically significant (Figure 9.d). During the subsequent time intervals (months 6-12, 12-18, and 18-24), the percentage of subjects with at least 1 flare was consistently and significantly lower in the febuxostat group than the placebo group. Over the entire study duration, the percentage of subjects with at least 1 flare was significantly lower in the febuxostat group than the placebo group (29.3% vs 41.4%, $p<0.05$). The proportion of subjects achieving target sUA of <6 mg/dL was significantly higher in those who were treated with febuxostat vs placebo (62.8% vs 5.7%; $p<0.001$).

Figure 9.d Reduction of Flares Following Treatment With Febuxostat vs Placebo Over 2 Years in Early Gout (TMX-67-204)



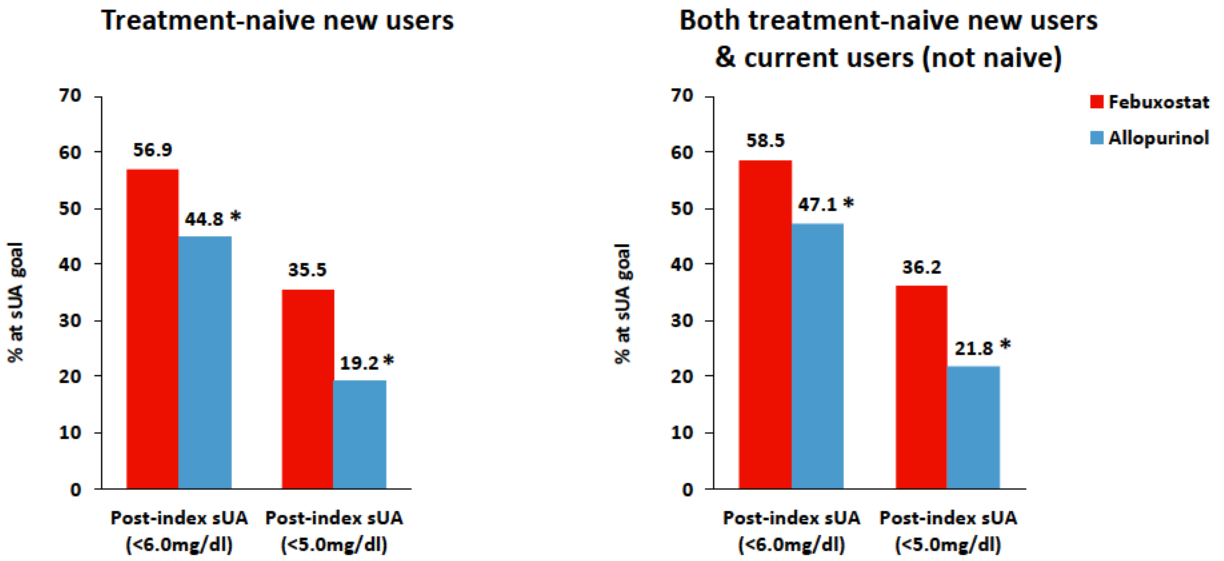
p-values for difference between treatment groups are from Fisher exact test
*, ** indicate statistical significance at the 0.05 or 0.01 level, respectively.

An additional benefit of ULT found in this study was MRI evidence for greater reduction in inflammation of the synovial lining of the index joint in febuxostat-treated than placebo-treated subjects (-0.43 vs -0.07; p <0.001). In summary, treat to target (sUA <6 mg/dL) with febuxostat reduced gout flares and improved MRI synovitis in subjects with early gout compared with placebo over a period of 2 years.

9.4 Clinical Efficacy in Real World Setting

Since the 2009 FDA approval, data have been published on the clinical effectiveness of febuxostat in real world settings and the role of febuxostat in the modern ULT care landscape. Singh et al, has evaluated the urate lowering effectiveness of febuxostat compared with allopurinol in a real world setting. This analysis used medical and pharmacy claims and laboratory data from a large US commercial and Medicare Advantage health plan from 2009 to 2012. The study sample included 2015 patients taking febuxostat and 14,025 patients taking allopurinol. In this clinical practice–based study, 83% of febuxostat users were on 40 mg/day and 97% of allopurinol users were on 300 mg/day or lower doses. In this real-world setting, a higher proportion of patients on febuxostat compared to allopurinol (56.9% vs 44.8%, p<0.001) achieved a target sUA of <6 mg/dL and <5 mg/dL (35.5 % vs 19.2%, p<0.001), respectively, based on postindex sUA levels [35].

Figure 9.e Clinical Efficacy of Febuxostat vs Allopurinol in a Real-World Setting (Proportion of Patients Achieving Target sUA)



Source: Singh et al [35].
sUA: serum uric acid.
The most common doses were 40 mg/day for febuxostat (83%), and 300 mg/day or lower dose for allopurinol (97%).
* p<0.001 febuxostat vs allopurinol.

Additionally, in a 13-year Taiwanese inception cohort study of CKD patients (n = 874), the sUA lowering effect was larger in febuxostat initiators (-3.71 mg/dL) than allopurinol initiators (-1.5 mg/dL) [69].

A prospective observational study (n = 106) at a gout clinic in the United Kingdom employed a nurse-led treat-to-target sUA approach (to enhance drug adherence), starting from allopurinol as the first-line ULT and febuxostat or uricosurics as the second-line ULT [70]. Over 1 year of follow-up, 92% achieved the therapeutic target (sUA ≤6 mg/dL); however, 21% of patients needed to switch their ULT from allopurinol to febuxostat (16%) or a uricosuric agent (5%). The reasons for switching were side effects (11%), treatment failure (8%), or concomitant drug interaction (2%). In a subsequent randomized study (n = 517), 95% of the nurse-led treat-to-target group (n = 255) with the same ULT sequential approach achieved the target sUA level (<6 mg/dL) over 2 years, with 14% using febuxostat and 1.6% using a uricosuric agent at Year 2 [71]. These data suggest that febuxostat has filled the unmet need for sUA control among 14% to 16% of gout patients needing a ULT, even after an intensive target-to-treat approach that maximizes allopurinol use with dose up-titration to 900 mg/day.

Of note, the approved febuxostat doses in Taiwan (80 mg) and the United Kingdom (80 and 120 mg) compared with the approved doses in the US (40 and 80 mg). Overall, the results from these studies conducted in a real-world setting demonstrate the benefit of febuxostat compared with allopurinol in the clinical management of hyperuricemia in patients with gout.

9.5 Efficacy Conclusion

The efficacy for febuxostat has been established based on previous clinical studies and in the real-world setting. Its effectiveness is particularly noteworthy in subjects with a high disease burden (sUA ≥10 mg/dL or tophi) or with renal impairment who are more difficult to treat populations in gout. Although the CARES study was not designed to assess efficacy, febuxostat demonstrated its ability to lower sUA levels, reduce gout flare over time, and decrease tophus size.

Overall, the data show the value of treating to sUA target with ULT in the improvement of clinical outcomes by reducing gout flares and achieving tophi resolution over time.

10.0 BENEFITS AND RISK ASSESSMENT

In order to provide a comprehensive benefit risk assessment for febuxostat, Takeda has used the structured approach and dimensions of the revised FDA Benefit Risk Framework (PDUFA VI Plan [FY 2018-2022]).

10.1 Analysis of Condition

Gout is a common form of inflammatory arthritis and when not treated or inadequately treated, can be a serious and debilitating disease, resulting in poor quality of life. It is characterized by flares of acute arthritis, chronic gouty arthropathy, tophi, and uric acid urolithiasis, and is associated with a broad range of comorbidities, including CV disease, CKD, and metabolic syndrome [2-4]. The most frequent initial clinical manifestation of gout is a flare of inflammatory arthritis, which develops over a few hours, usually involves a single LE joint, and is severely disabling due to extreme pain, swelling, and loss of joint function. In most patients, the initial attack resolves spontaneously and completely within a week or 2 and, in most instances, recurs intermittently and progressively more often. The underlying metabolic aberration in gout is hyperuricemia, an elevation in plasma or sUA level ≥6.8 mg/dL, which signals a risk for gout through urate crystal formation and deposition. Over time, the crystal deposition and inflammation can result in progressive joint damage and erosion, with the formation of tophi, which can be deforming and disabling. Patients with gout also have a higher risk of CV disease, renal disease, and mortality.

10.2 Current Treatment Options

There are few treatment options for gout in the US and each agent has limitations and safety risks. With these few treatment options, effective management of the disease is challenging. There are 3 categories of ULT:

- XOI: recommended as first-line ULT, a role most often fulfilled with allopurinol, or alternatively, febuxostat.
- Uricosuric agents: In the event of failure to reach goal urate level with a XOI or intolerance, recommended second-line therapies are combination XOI/uricosuric therapy with lesinurad (200 mg/day only) or probenecid. Alternatively, second-line therapy also includes probenecid monotherapy. Probenecid requires multiple daily dosing, and often, several titration steps to achieve goal urate levels. This agent has many drug interactions and limited urate-lowering efficacy in patients with moderate and severe renal impairment (eCrCl <60 mL/min).
- Biological uricolytic therapy with pegloticase is third-line therapy and is reserved for patients with clinically far advanced gout and failure or intolerance to alternative ULT. Pegloticase therapy requires biweekly IV administration and can cause anaphylaxis and must be administered in a healthcare setting.

Of these limited options, the XOI allopurinol has been the mainstay for treatment of chronic gout for decades. Allopurinol is approved at doses up to 800 mg daily; however, it is rarely dosed over 300 mg daily because of the multistep titration requiring repeat serum urate measurements

and therefore is often suboptimal. In addition, higher doses of allopurinol (>300 mg/day) have not been widely used out of concern for adverse drug reactions, especially rashes and, in particular AHS, a frequently fatal hypersensitivity reaction. AHS is rare in the white population, but the incidence is higher in Asian American and African American populations. Since patients with renal impairment may develop toxicities at higher doses, it is usually recommended that the dose of allopurinol be reduced for patients with a decreased creatinine clearance; this further reduces the efficacy in this population.

On the basis of QuintilesIMS data (2013-2017), febuxostat is used as a first-line treatment in approximately 7% of patients with gout, with allopurinol used in the majority of patients. IMS data also indicate that patients cycle through allopurinol and febuxostat to achieve benefit demonstrating the need for flexibility for physicians to prescribe based on patient need.

10.3 Benefit

Febuxostat is efficacious in lowering sUA in patients with gout. The dosing schedule is a simplified 1-step titration as needed to achieve sUA targets. Febuxostat has demonstrated the ability to achieve sUA targets of <6.0 and/or <5.0 mg/dL better than commonly prescribed doses of allopurinol (≤300 mg/day) in current clinical practice, including in patients with sUA levels ≥10 mg/dL or who have tophi, and patients with renal impairment. Additionally, febuxostat decreases acute flares, and reduces tophus size over time, through persistent long-term urate lowering effects.

The use of allopurinol doses >300 mg daily is very uncommon, reflecting many patient and caregiver concerns about this agent, including safety of the drug in patients with renal impairment and recognition of allopurinol as one of the more common agents associated with severe hypersensitivity reactions. Thus, the results of febuxostat urate-lowering monotherapy, particularly in patients with gout and impaired renal function, and its potential use in combination XOI/uricosuric combined therapy, identifies it as an important alternative to allopurinol.

A high percentage of patients with gout have some degree of renal impairment. Unlike allopurinol, a dose adjustment is not required for patients with mild to moderate renal impairment, and febuxostat 40 mg can be used in patients with severe renal impairment.

Febuxostat is also an alternative to allopurinol in the population who are positive for the HLA-B5801 allele [45]. These patients are at high risk for AHS induced by allopurinol and its metabolite oxypurinol. AHS is accompanied by significant mortality risk.

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

10.4 Risk and Risk Management

10.4.1 Risk

Febuxostat has been evaluated in more than 18,368 subjects in company-sponsored clinical studies and has more than 15 million PY of cumulative exposure. The safety profile of febuxostat is well characterized. A thorough and comprehensive evaluation of the CV safety has been conducted from the development program, CARES, and postmarketing surveillance.

In the phase 3 APEX and FACT studies, APTC events (CV death, nonfatal MI, nonfatal stroke) were numerically low, but there was an imbalance in the rate of events for febuxostat 80 and 120 mg compared with allopurinol or placebo. Because of the small numbers of events in each study arm, there was uncertainty whether the adverse events represented a genuine safety signal or whether they occurred by chance. To address this issue, the CONFIRMS study was conducted with febuxostat 40 and 80 mg and APTC events were prospectively adjudicated. This study did not show an increase in serious CV events.

In a pooled analysis of the randomized phase 3 studies (APEX, FACT, CONFIRMS), a numerical imbalance was observed in the number of CV thromboembolic events in the composite of CV death, nonfatal MI, and nonfatal stroke in subjects treated with febuxostat compared with allopurinol. The rate of CV death for the combined febuxostat-treated subjects was similar to that for the allopurinol treatment group.

Febuxostat was approved with a Warnings and Precautions for Cardiovascular Events highlighting the rates of CV events. In addition, there was a postmarketing requirement to conduct a CVOT (CARES) to determine whether febuxostat was associated with an increase in the risk of serious adverse CV outcomes compared with allopurinol.

The CARES study demonstrated that febuxostat is noninferior to allopurinol for the MACE composite primary endpoint in subjects with gout and a high CV risk profile [8]. The study also showed febuxostat is not different for individual components of MACE for nonfatal MI, nonfatal stroke, and unstable angina with urgent coronary revascularization compared with allopurinol. However, febuxostat showed a higher rate of CV death compared with allopurinol. The all-cause mortality rate was also higher with febuxostat compared with allopurinol, largely due to these differences in CV death. Following comprehensive clinical assessments and exploratory analyses, Takeda has been unable to determine any contributing factors or a population at risk for a higher rate of CV death in the CARES study. Furthermore, the risk of CV mortality for febuxostat and allopurinol compared with the untreated gout population cannot be defined as there was no placebo group in this study.

A retrospective and comprehensive search of the global safety database for febuxostat was conducted and did not identify a signal for CV events or CV death with febuxostat. No safety signal had been observed through routine pharmacovigilance activities, including regular signal detection activities.

Considering the totality of the evidence, including the lack of concordance between the individual MACE components, the inability to explain the finding and the absence of biological plausibility, there remains uncertainty about the reliability of the observation.

10.4.2 Risk Management

Febuxostat continues to be an important treatment option in the management of hyperuricemia in patients with gout. Considering the seriousness of the disease, the limited treatment options, the clinical use of febuxostat over 10 years and its safety profile, including the totality of the CV safety data, the benefit-risk assessment for febuxostat remains positive.

The CARES data has been widely disseminated to the medical community over the last several months. The primary and secondary endpoint study results of the CARES study were published in the *New England Journal of Medicine and* presented at the American College of Cardiology congress in March 2018 and at the ACR Conference in October 2018 to facilitate scientific exchange of the data and ensure that the latest information is publicly available [9]. Takeda will continue to share the CARES findings with the medical community.

The seriousness of the observation in CARES makes it important that physicians are informed with the best available information so they can consider the benefits and risks of febuxostat compared with other treatment options for each individual patient. Therefore, Takeda proposes the prescribing information is updated with the CARES data to include CV death in the Warnings and Precautions section, describe the CARES study results in the clinical studies section, and all other relevant sections. Specific labeling language will be discussed with FDA during labeling review.

Takeda will communicate these important updates following label approval, via distribution of a dear healthcare provider letter to HCPs, pharmacies and professional societies.

Takeda continues to evaluate the literature and postmarketing surveillance for the continuous assessment of CV data reported for febuxostat. In addition, Takeda commits to provide the FDA the outcome of the ongoing European FAST CV safety study upon its conclusion and make any further appropriate adjustments to its risk management plan accordingly.

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Appendix 1 Selection of Study Population in the CARES Study

Inclusion Criteria

Subject eligibility was determined according to the following criteria:

1. The subject or the subject's legally acceptable representative signed and dated a written, informed consent form prior to the initiation of any study procedures.

1. The subject was male ≥50 years of age or female ≥55 years of age and at least 2 years postmenopausal.

2. The subject had a history of major CV or cerebrovascular disease including at least 1 of the following:

- MI.
- Hospitalized unstable angina.
- Cardiac or cerebrovascular revascularization procedure.
- Stroke.
- Hospitalized TIA.
- Peripheral vascular disease (ankle brachial index ≤0.6, revascularization, and/or well-documented history of claudication).
- History of diabetes mellitus with evidence of microvascular or macrovascular disease (retinopathy, neuropathy, nephropathy, small vessel vascular diseases).

3. The subject had a history or presence of gout defined as having one or more of the American Rheumatism Association criteria for the diagnosis of gout [72]:

- A tophus proven to contain urate crystals by chemical or polarized light microscopic means, AND/OR
- Characteristic urate crystals in the joint fluid, AND/OR
- History of at least 6 of the following clinical, laboratory, and x-ray phenomena:
  - More than 1 attack of acute arthritis.
  - Maximum inflammation developed within 1 day.
  - Monoarticular arthritis.
  - Redness observed over joints.
  - First metatarsophalangeal joint painful or swollen.
  - Unilateral first metatarsophalangeal joint attack.
  - Unilateral tarsal joint attack.
  - Tophus (proven or suspected).

- Hyperuricemia.
- Asymmetric swelling within a joint on x-ray.
- Subcortical cysts without erosions on x-ray.
- Joint fluid culture negative for organisms during attack.

4. The subjects must have had either:

- An sUA level ≥7.0 mg/dL (≥416 μmol/L) at the screening visit **OR**
- An sUA level ≥6.0 mg/dL (≥354 μmol/L) at the screening visit **AND** inadequately controlled gout (≥1 flare in the 12 months before screening and/or the presence of tophi).

5. The subject was capable of understanding and complying with protocol requirements.

Exclusion Criteria

Any subject who met any of the following criteria did not qualify for entry into the study:

1. The subject had secondary hyperuricemia (eg, due to myeloproliferative disorder, or organ transplant).
2. The subject had a history of xanthinuria.
3. The subject had received ULT (ie, febuxostat, allopurinol, probenecid, etc.) or excluded medication less than 7 days prior to Study Day 1/randomization visit.
4. The subject had a known hypersensitivity to febuxostat or allopurinol or any components of their formulation.
5. The subject had active peptic ulcer disease.
6. The subject had a history of cancer (other than basal cell carcinoma of the skin) within 5 years prior to the first dose of study medication.
7. The subject had MI or stroke within 60 days prior to the screening visit.
8. The subject had ALT and/or AST values greater than 2 × ULN during the screening period.
9. The subject had a significant medical condition and/or conditions that would interfere with the treatment, safety, or compliance with the protocol.
10. The subject had a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 5 years prior to the screening visit or the subject consumes >14 alcoholic beverages per week.
11. The subject received any investigational medicinal product within the 30 days prior to the screening visit and throughout the study. In addition, the subject had been previously randomized in this study and received at least 1 dose of double blind study drug treatment.

12. The subject's eCrCl was <30 mL/min, where eCrCl was calculated using the Cockcroft and Gault formula based on ideal body weight (IBW), as provided below:

$$eCrCl = \frac{(140 - \text{age [yr]}) \times (\text{IBW [kg]})}{72 \times (\text{serum creatinine [mg/dL]})} \text{ (women multiply by 0.85)}$$

    Where IBW was 50 kg for men and 45.5 kg for women, plus 2.3 kg for each inch in height greater than 5 feet (60 inches).

13. The subject was an immediate family member, study site employee, or was in a dependent relationship with a study site employee who was involved in conduct of this study (eg, spouse, parent, child, sibling) or may have consented under duress.

14. The subject was required to take excluded medications.

15. The subject had a known history of infection with hepatitis B, hepatitis C, or HIV.

Appendix 2 CARES Study Design

The CARES study was a phase 3B multicenter, randomized, double-blind, active-controlled study designed to evaluate the CV safety of febuxostat compared with allopurinol in subjects with gout and significant CV comorbidities.

Subjects were screened at Day -7 for entry. Subjects with CV comorbidities, gout, and 1) an sUA ≥7 mg/dL or 2) with an sUA ≥6 mg/dL AND at least 1 flare in the 12 months before the screening visit and/or the presence of tophi and who meet the other selection criteria were enrolled.

On Study Day 1/randomization visit, eligible subjects were randomized in a 1:1 ratio to receive either febuxostat QD or allopurinol QD. Randomization was stratified based on baseline renal function: subjects with normal renal function or mild renal impairment (eCrCl ≥60 mL/min) versus subjects with moderate renal impairment (eCrCl ≥30 but <60 mL/min].

Subjects randomized to febuxostat initially received the 40 mg dose QD. Subjects remained on 40 mg for the remainder of the study if their sUA was <6.0 mg/dL at the Week 2 Visit (±3 days). If their sUA was ≥6.0 mg/dL at the Week 2 Visit (±3 days), they received febuxostat 80 mg QD at Week 4 visit (±3 days), and remained on this dose for the remainder of the study. No dose adjustment was made in the febuxostat group on the basis of renal function.

Subjects randomized to allopurinol who had normal renal function or mild renal impairment (eCrCl ≥60 mL/min) initially received allopurinol 300 mg QD with the dose increased in 100 mg increments monthly until either a sUA <6.0 mg/dL or an allopurinol dose of 600 mg QD was achieved. Subjects randomized to allopurinol who had moderate renal impairment (eCrCl ≥30 but <60 mL/min) initially received allopurinol 200 mg QD with the dose increased in 100 mg increments monthly until either a sUA <6.0 mg/dL or an allopurinol dose of 400 mg QD was achieved.

To maintain the double-blind nature of the study, febuxostat and allopurinol tablets were over-encapsulated, and matching placebo capsules were manufactured that were identical in appearance. Subjects orally self-administered 2 capsules each morning in the appropriate combination for their assigned dose and treatment.

Serum urate levels were unblinded to the investigator and Takeda through the Week 10 visit of the study to facilitate dose increases based on sUA response. After the Week 10 visit sUA measurements were blinded to Takeda and the investigator. All dose titrations were completed by the Month 3 visit. The interactive voice-activated response system/interactive web-activated response system managed the treatment assignment at randomization and throughout the study medication treatment period.

Subjects currently on ULT discontinued treatment at the Day -7 screening visit and began colchicine 0.6 mg QD for gout flare prophylaxis. Subjects not on ULT began colchicine 0.6 mg QD on the Day 1/randomization visit. All subjects received gout flare prophylaxis for the first 6 months of the study medication treatment period. Alternatively, if colchicine was not tolerated and the subject's eCrCl was ≥50 mL/min, they were administered naproxen 250 mg twice daily

with lansoprazole 15 mg QD. If a subject was maintained on an appropriate dose (as determined by the investigator) of another proton pump inhibitor (PPI) other than lansoprazole, he/she could have continued treatment with it during this study. In instances when subjects could not receive colchicine or naproxen, other NSAIDs or prednisone were provided at the investigator's discretion in accordance with the stated guidelines listed under the Excluded Medications and Treatments section of the protocol. In the event that colchicine, naproxen or other NSAIDs, PPIs, or prednisone were not tolerated or were contraindicated, the investigator may have chosen not to use prophylaxis but to manage the subject's gout flares as they occurred. Alternatively, if colchicine 0.6 mg daily was not tolerated by the subject, 0.6 mg every other day could have been used. Following the Day 1 visit, subjects returned for study visits during the first 3 months of the study based on the subject's sUA response. Once a subject's sUA was <6.0 mg/dL, there were no further visits until Month 3.

All subjects returned at Week 2 for measurement of sUA and for a Week 4 and Month 3 visit. If the Week 2 sUA level was <6.0 mg/dL, study medication was dispensed to the subject at Week 4, and the next visit occurred at Month 3. If the Week 2 sUA level was ≥6.0 mg/dL, study medication was dispensed to the subject at Week 4, and the next visit occurred at Week 6.

For the subset of subjects who had a Week 6 visit, if the Week 6 sUA level was <6.0 mg/dL, study medication was dispensed to the subject at Week 8, and the next visit occurred at Month 3. If the Week 6 sUA level was ≥6.0 mg/dL, study medication was dispensed to the subject at Week 8 and the next visit occurred at Week 10.

For the subset of subjects who had a Week 10 visit, study medication was dispensed to the subject at the Month 3 visit. After the Month 3 visit, no further dose adjustments were made. All subjects had a Month 3 and Month 6 visit.

Following the Month 6 visit, all subjects had visits every 6 months for the duration of the study. In addition, subjects with moderate renal impairment (eCrCl ≥30 but <60 mL/min) and/or subjects who were elderly (≥65 years of age) had visits at Month 9 and Month 15 to monitor the liver function tests.

Subjects who discontinued study drug had the option to (1) continue study participation (off study drug) until the study was completed, or (2) discontinue completely from the study. Subjects who discontinued study drug were strongly encouraged to continue participation until the study was completed. Subjects who were withdrawn from study medication treatment but had not withdrawn consent were contacted every 2 months for the duration of the study or until the subject experienced a CV event that was positively adjudicated as a MACE.

Appendix 3 Demographic and Other Baseline Characteristics

Summary of Demographic and Baseline Characteristics

Characteristic	Febuxostat (N = 3098)	Allopurinol (N = 3092)	Total (N = 6190)
Age (years)			
Mean (SD)	64.6 (8.58)	65.0 (8.49)	64.8 (8.53)
Minimum, maximum	49, 93	44, 90	44, 93
<65 years, n (%)	1584 (51.1)	1506 (48.7)	3090 (49.9)
65 to <75 years, n (%)	1094 (35.3)	1135 (36.7)	2229 (36.0)
≥75 years, n (%)	420 (13.6)	451 (14.6)	871 (14.1)
Sex, n (%)			
Male	2604 (84.1)	2592 (83.8)	5196 (83.9)
Female	494 (15.9)	500 (16.2)	994 (16.1)
Race, n (%)			
American Indian or Alaska Native	262 (8.5)	234 (7.6)	496 (8.0)
Asian	92 (3.0)	96 (3.1)	188 (3.0)
Black or African American	552 (17.8)	593 (19.2)	1145 (18.5)
Native Hawaiian or Other Pacific Islander	13 (0.4)	14 (0.5)	27 (0.4)
White	2160 (69.7)	2140 (69.2)	4300 (69.5)
Other	19 (0.6)	15 (0.5)	34 (0.5)
Ethnicity, n (%)			
Hispanic or Latino	539 (17.4)	521 (16.8)	1060 (17.1)
Not Hispanic or Latino	2559 (82.6)	2571 (83.2)	5130 (82.9)
Height (cm)			
Mean (SD)	172.9 (9.54)	173.0 (9.77)	173.0 (9.65)
Minimum, maximum	122, 207	112, 203	112, 207
Weight (kg) N	3098	3087	6185
Mean (SD)	100.5 (22.47)	100.3 (22.89)	100.4 (22.68)
Minimum, maximum	44,210	45,220	44,220

Footnotes are on last table page.

Summary of Demographic and Baseline Characteristics (continued)

Characteristic	Febuxostat (N = 3098)	Allopurinol (N = 3092)	Total (N = 6190)
BMI (kg/m²) N	3098	3087	6185
Median	32.5	32.1	32.3
BMI categories (kg/m²), n (%)			
<25	201 (6.5)	201 (6.5)	402 (6.5)
25-30	844 (27.2)	862 (27.9)	1706 (27.6)
≥30	2053 (66.3)	2024 (65.5)	4077 (65.9)
Smoking history, n (%)			
Never smoked	1175 (37.9)	1124 (36.4)	2299 (37.1)
Ex-smoker	1533 (49.5)	1553 (50.2)	3086 (49.9)
Current smoker	390 (12.6)	415 (13.4)	805 (13.0)
Alcohol history, n (%)			
Never drank	792 (25.6)	784 (25.4)	1576 (25.5)
Ex-drinker	805 (26.0)	812 (26.3)	1617 (26.1)
Current drinker	1501 (48.5)	1496 (48.4)	2997 (48.4)
Renal function, n (%) [a]			
Moderately impaired	1636 (52.8)	1631 (52.7)	3267 (52.8)
Mildly impaired	1217 (39.3)	1231 (39.8)	2448 (39.5)
Normal	239 (7.7)	228 (7.4)	467 (7.5)
History of kidney stone, n (%)			
Yes	627 (20.2)	627 (20.3)	1254 (20.3)
No	2471 (79.8)	2465 (79.7)	4936 (79.7)
Use of low dose aspirin, n (%) [b]			
Yes	1496 (48.3)	1481 (47.9)	2977 (48.1)
No	1602 (51.7)	1611 (52.1)	3213 (51.9)
Use of any dose of aspirin, n (%)			
Yes	1894 (61.1)	1933 (62.5)	3827 (61.8)
No	1204 (38.9)	1159 (37.5)	2363 (38.2)
Use of NSAIDs, n (%)			
Yes	856 (27.6)	908 (29.4)	1764 (28.5)
No	2242 (72.4)	2184 (70.6)	4426 (71.5)
Use of clopidogrel and other antiplatelet drugs, n (%)			
Yes	599 (19.3)	627 (20.3)	1226 (19.8)
No	2499 (80.7)	2465 (79.7)	4964 (80.2)

BMI: body mass index; eCrCl: estimated creatinine clearance; NSAID: nonsteroidal anti-inflammatory drug.
[a] Moderate renal impairment: eCrCl = 30 to 59 mL/min; mild renal impairment: eCrCl = 60 to 89 mL/min; normal: eCrCl ≥90 mL/min. Seven subjects with Baseline eCrCl <30 mL/min and 1 subject with missing baseline eCrCl
[b] Dosing <325 mg aspirin per day is considered as low-dose aspirin.

Gout History

Characteristic	Febuxostat (N = 3098)	Allopurinol (N = 3092)	Total (N = 6190)
Baseline sUA (mg/dL)			
Mean (SD)	8.74 (1.687)	8.69 (1.671)	8.71 (1.679)
Baseline sUA categories (mg/dL), n (%)			
<7.0	412 (13.3)	436 (14.1)	848 (13.7)
7.0 to <8.0	631 (20.4)	620 (20.1)	1251 (20.2)
8.0 to <9.0	735 (23.7)	759 (24.5)	1494 (24.1)
9.0 to <10.0	666 (21.5)	646 (20.9)	1312 (21.2)
≥10.0	654 (21.1)	631 (20.4)	1285 (20.8)
Number of gout flares during the past year, n (%)			
1 to 3	1880 (60.7)	1842 (59.6)	3722 (60.1)
4 to 6	544 (17.6)	544 (17.6)	1088 (17.6)
>6	356 (11.5)	409 (13.2)	765 (12.4)
Years since gout diagnosis, N [a]	3097	3092	6189
Mean (SD)	11.75 (11.425)	11.87 (11.192)	11.81 (11.309)
Time since last gout flare			
<1 month ago	1017 (32.8)	978 (31.6)	1995 (32.2)
1 to <4 months ago	981 (31.7)	1009 (32.6)	1990 (32.1)
4 to <6 months ago	311 (10.0)	353 (11.4)	664 (10.7)
6 to <12 months ago	471 (15.2)	455 (14.7)	926 (15.0)
≥1 year ago	317 (10.2)	296 (9.6)	613 (9.9)

Footnotes are on last table page.

Gout Disease History

Characteristic	Febuxostat (N = 3098)	Allopurinol (N = 3092)	Total (N = 6190)
Prior ULTs			
No	1045 (33.7)	1044 (33.8)	2089 (33.7)
Yes [b]	1914 (61.8)	1914 (61.9)	3828 (61.8)
Febuxostat	134 (4.3)	130 (4.2)	264 (4.3)
Allopurinol	1738 (56.1)	1742 (56.3)	3480 (56.2)
Probenecid	37 (1.2)	36 (1.2)	73 (1.2)
Other	5 (0.2)	6 (0.2)	11 (0.2)
Baseline tophus			
No	2430 (78.4)	2442 (79.0)	4872 (78.7)
Yes	668 (21.6)	650 (21.0)	1318 (21.3)

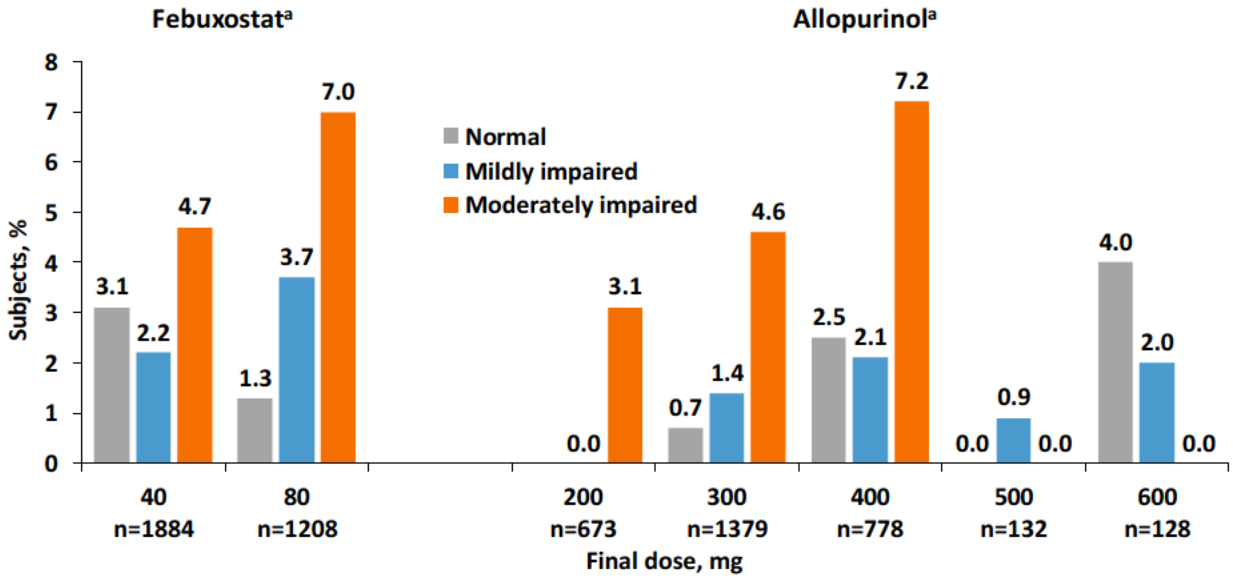
sUA: serum uric acid; ULT: urate-lowering therapy.
[a] Years are calculated based on first dose of double-blind study drug.
[b] Subject was counted only once if >1 ULT was taken.

CV History

History	Febuxostat (N = 3098)	Allopurinol (N = 3092)	Total (N = 6190)
Myocardial infarction	1197 (38.6)	1231 (39.8)	2428 (39.2)
Hospitalized unstable angina	855 (27.6)	869 (28.1)	1724 (27.9)
Cardiac revascularization	1129 (36.4)	1182 (38.2)	2311 (37.3)
Cerebral revascularization	69 (2.2)	54 (1.7)	123 (2.0)
Stroke	460 (14.8)	410 (13.3)	870 (14.1)
Hospitalized transient ischemic attack	362 (11.7)	291 (9.4)	653 (10.5)
Peripheral vascular disease [a]	412 (13.3)	375 (12.1)	787 (12.7)
Ankle brachial index ≤0.6	207 (6.7)	179 (5.8)	386 (6.2)
Revascularization	125 (4.0)	112 (3.6)	237 (3.8)
History of claudication	242 (7.8)	226 (7.3)	468 (7.6)
Deep vein thrombosis	157 (5.1)	128 (4.1)	285 (4.6)
Pulmonary embolism	77 (2.5)	59 (1.9)	136 (2.2)
Coronary artery bypass graft procedure	706 (22.8)	760 (24.6)	1466 (23.7)
Percutaneous transluminal coronary angioplasty	780 (25.2)	840 (27.2)	1620 (26.2)
Cardiac arrhythmia	743 (24.0)	779 (25.2)	1522 (24.6)
Have a pacemaker or defibrillator	297 (9.6)	327 (10.6)	624 (10.1)
Congestive heart failure [a]	622 (20.1)	631 (20.4)	1253 (20.2)
History of diabetes mellitus [a]	1710 (55.2)	1699 (54.9)	3409 (55.1)
Retinopathy	157 (5.1)	162 (5.2)	319 (5.2)
Neuropathy	944 (30.5)	939 (30.4)	1883 (30.4)
Nephropathy	351 (11.3)	371 (12.0)	722 (11.7)
Small vessel vascular disease	73 (2.4)	79 (2.6)	152 (2.5)
CV risk factors			
Hypertension	2864 (92.4)	2851 (92.2)	5715 (92.3)
Hyperlipidemia	2678 (86.4)	2702 (87.4)	5380 (86.9)

CV: cardiovascular.
CV histories that stopped at or before the date of informed consent.
[a] Subject was counted only once if >1 category in the list selected.

Appendix 4 CV Death by Final Titrated Treatment Dose and Renal Function



CV: cardiovascular; sUA: serum uric acid.
[a] Febuxostat dose titrated based on sUA. Allopurinol dose titrated based on sUA and renal function.