

**Table 17 : Proportion of Subjects Whose Last 3 Serum Urate Levels Were <6.0 mg/dL by Race - ITT Subjects (Phase 3 Pivotal Studies)**

Race	Placebo		Febuxostat 80 mg QD <sup>a,m</sup>		Febuxostat 120 mg QD <sup>a,#</sup>		Febuxostat 240 mg QD		Allopurinol 300/100 mg QD	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
Caucasian	0/108	(0%)	205/388	(53%)	280/412	(68%)	77/107	(72%)	91/400	(23%)
Non-Caucasian	0/26	(0%)	57/129	(44%)	49/107	(46%)	15/27	(56%)	22/119	(18%)

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

# Statistically significant difference between subgroups within this treatment group ( $p \leq 0.05$ ) using a CMH test adjusting for study.

a Statistically significant difference versus allopurinol 300/100 mg QD ( $p \leq 0.05$ ) using a CMH test adjusting for subgroup and study.

m Statistically significant difference versus febuxostat 120 mg QD ( $p \leq 0.05$ ) using a CMH test adjusting for subgroup and study.

Cross-reference: Module 5.3.5.3.1, Statistical Table 3.3

**Table 18: Proportion of Subjects Whose Last 3 Serum Urate Levels Were <6.0 mg/dL by Baseline Serum Creatinine - ITT Subjects (Phase 3 Pivotal Studies)**

Baseline Serum Creatinine	Placebo		Febuxostat 80 mg QD <sup>a,m</sup>		Febuxostat 120 mg QD <sup>a</sup>		Febuxostat 240 mg QD		Allopurinol 300/100 mg QD	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
$\leq 1.5$ mg/dL	0/131	(0%)	257/506	(51%)	322/504	(64%)	88/127	(69%)	112/508	(22%)
$> 1.5$ mg/dL	0/3	(0%)	5/11	(45%)	7/15	(47%)	4/7	(57%)	1/11	(9%)

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

a Statistically significant difference versus allopurinol 300/100 mg QD ( $p \leq 0.05$ ) using a CMH test adjusting for subgroup and study.

m Statistically significant difference versus febuxostat 120 mg QD ( $p \leq 0.05$ ) using a CMH test adjusting for subgroup and study.

Cross-reference: Module 5.3.5.3.1, Statistical Table 3.3

*Reviewers comments: there are too few subjects in the creatinine greater than 1.5 group to reach any firm conclusions.*

**Table 19 : Proportion of Subjects Whose Last 3 Serum Urate Levels Were <6.0 mg/dL by Baseline Calculated Creatinine Clearance – ITT Subjects (Phase 3 Pivotal Studies)**

Baseline Calculated Creatinine Clearance	Placebo		Febuxostat 80 mg QD <sup>a,#,m</sup>		Febuxostat 120 mg QD <sup>a</sup>		Febuxostat 240 mg QD		Allopurinol 300/100 mg QD <sup>#</sup>	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
<50 mL/min	0/9	(0%)	19/28	(68%)	20/26	(77%)	8/14	(57%)	16/35	(46%)
50-<80 mL/min	0/36	(0%)	92/153	(60%)	102/157	(65%)	27/37	(73%)	43/145	(30%)
80-<120 mL/min	0/65	(0%)	122/261	(47%)	175/280	(63%)	48/68	(71%)	48/269	(18%)
≥120 mL/min	0/24	(0%)	29/75	(39%)	32/55	(58%)	9/15	(60%)	6/66	(9%)
Missing	0/0	--	0/0	--	0/1	(0%)	0/0	--	0/4	(0%)

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

Note: Baseline calculated  $Cl_{cr}$  was based on ideal body weight.

# Statistical significant difference among subgroups within this treatment group ( $p \leq 0.05$ ) using a CMH test adjusting for study.

a Statistically significant difference versus allopurinol 300/100 mg QD ( $p \leq 0.05$ ) using a CMH test adjusting for subgroup and study.

m Statistically significant difference versus febuxostat 120 mg QD ( $p \leq 0.05$ ) using a CMH test adjusting for subgroup and study.

Cross-reference: Module 5.3.5.3.1, Statistical Table 3.3

**Table 20: Proportion of Subjects Whose Last 3 Serum Urate Levels Were <6.0 mg/dL by Baseline Serum Urate - ITT Subjects (Phase 3 Pivotal Studies)**

Baseline Serum Urate	Placebo		Febuxostat 80 mg QD <sup>a,#,m</sup>		Febuxostat 120 mg QD <sup>a#</sup>		Febuxostat 240 mg QD		Allopurinol 300/100 mg QD <sup>#</sup>	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
<9.0 mg/dL	0/34	(0%)	83/136	(61%)	107/144	(74%)	24/36	(67%)	54/142	(38%)
9.0-<10.0 mg/dL	0/51	(0%)	90/165	(55%)	119/161	(74%)	35/48	(73%)	41/177	(23%)
≥10.0 mg/dL	0/49	(0%)	89/216	(41%)	103/214	(48%)	33/50	(66%)	18/200	(9%)

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

# Statistical significant difference among subgroups within this treatment group ( $p \leq 0.05$ ) using a CMH test adjusting for study.

a Statistically significant difference versus allopurinol 300/100 mg QD ( $p \leq 0.05$ ) using a CMH test adjusting for subgroup and study.

m Statistically significant difference versus febuxostat 120 mg QD ( $p \leq 0.05$ ) using a CMH test adjusting for subgroup and study.

Cross-reference: Module 5.3.5.3.1, Statistical Table 3.3

**Table 21 : Proportion of Subjects Whose Last 3 Serum Urate Levels Were <6.0 mg/dL by Previous Use of Urate-Lowering Therapy – ITT Subjects (Phase 3 Pivotal Studies)**

Previous Use of Urate-Lowering Therapy	Placebo		Febuxostat 80 mg QD <sup>a,m</sup>		Febuxostat 120 mg QD <sup>a</sup>		Febuxostat 240 mg QD		Allopurinol 300/100 mg QD	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
Prior Use	0/32	(0%)	116/199	(58%)	135/202	(67%)	33/49	(67%)	43/201	(21%)
No Prior Use	0/102	(0%)	146/318	(46%)	194/317	(61%)	59/85	(69%)	70/318	(22%)

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

- # Statistically significant difference between subgroups within this treatment group ( $p \leq 0.05$ ) using a CMH test adjusting for study.
- a Statistically significant difference versus allopurinol 300/100 mg QD ( $p \leq 0.05$ ) using a CMH test adjusting for subgroup and study.
- m Statistically significant difference versus febuxostat 120 mg QD ( $p \leq 0.05$ ) using a CMH test adjusting for subgroup and study.

Cross-reference: Module 5.3.5.3.1, Statistical Table 3.3

**Table 22 : Proportion of Subjects Whose Last 3 Serum Urate Levels Were <6.0 mg/dL by History of Renal Calculi - ITT Subjects (Phase 3 Pivotal Studies)**

History of Renal Calculi	Placebo		Febuxostat 80 mg QD <sup>a,m</sup>		Febuxostat 120 mg QD <sup>a</sup>		Febuxostat 240 mg QD		Allopurinol 300/100 mg QD	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
History of Calculi	0/2	(0%)	30/52	(58%)	22/39	(56%)	1/2	(50%)	9/46	(20%)
No History of Calculi	0/132	(0%)	232/465	(50%)	307/480	(64%)	91/132	(69%)	104/473	(22%)

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

- a Statistically significant difference versus allopurinol 300/100 mg QD ( $p \leq 0.05$ ) using a CMH test adjusting for subgroup and study.
- m Statistically significant difference versus febuxostat 120 mg QD ( $p \leq 0.05$ ) using a CMH test adjusting for subgroup and study.

Cross-reference: Module 5.3.5.3.1, Statistical Table 3.3

**Table 23: Proportion of Subjects Whose Last 3 Serum Urate Levels Were <6.0 mg/dL by Low-Dose Aspirin Use - ITT Subjects (Phase 3 Pivotal Studies)**

Low-dose Aspirin Use	Placebo		Febuxostat 80 mg QD <sup>a,m</sup>		Febuxostat 120 mg QD <sup>a</sup>		Febuxostat 240 mg QD		Allopurinol 300/100 mg QD <sup>#</sup>	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
Yes	0/30	(0%)	56/86	(65%)	59/90	(66%)	27/34	(79%)	25/69	(36%)
No	0/104	(0%)	206/431	(48%)	270/429	(63%)	65/100	(65%)	88/450	(20%)

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

- # Statistically significant difference between subgroups within this treatment group ( $p \leq 0.05$ ) using a CMH test adjusting for study.
- a Statistically significant difference versus allopurinol 300/100 mg QD ( $p \leq 0.05$ ) using a CMH test adjusting for subgroup and study.
- m Statistically significant difference versus febuxostat 120 mg QD ( $p \leq 0.05$ ) using a CMH test adjusting for subgroup and study.

Cross-reference: Module 5.3.5.3.1, Statistical Table 3.3

**Table 24 : Proportion of Subjects Whose Last 3 Serum Urate Levels Were <6.0 mg/dL by Alcohol Use - ITT Subjects (Phase 3 Pivotal Studies)**

Alcohol Use	Placebo		Febuxostat 80 mg QD <sup>a,m</sup>		Febuxostat 120 mg QD <sup>a</sup>		Febuxostat 240 mg QD		Allopurinol 300/100 mg QD	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
Non-/Ex-Drinker	0/47	(0%)	93/171	(54%)	122/189	(65%)	37/55	(67%)	31/156	(20%)
Drinker	0/87	(0%)	169/346	(49%)	207/330	(63%)	55/79	(70%)	82/363	(23%)

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

- a Statistically significant difference versus allopurinol 300/100 mg QD ( $p \leq 0.05$ ) using a CMH test adjusting for subgroup and study.
- m Statistically significant difference versus febuxostat 120 mg QD ( $p \leq 0.05$ ) using a CMH test adjusting for subgroup and study.

Cross-reference: Module 5.3.5.3.1, Statistical Table 3.3

### 6.1.5 Clinical Microbiology

There is no clinical microbiology data provided to review.

### 6.1.6 Efficacy Conclusions

Based on the data provided, it can be concluded that febuxostat demonstrated efficacy in lowering serum urate levels in patients with gout. All doses studied showed efficacy and even superiority when compared to allopurinol. However, the data does not support

The sponsor should provide additional data in regards to the 40 mg dose and the dose. Based on results of the sole phase II trial, the 40 mg dose appears efficacious (based on modeling performed by clinical pharmacology reviewers, febuxostat 40 mg should be comparable to allopurinol 300 mg) and should be further studied as a lower dose with potentially greater safety. Based on results of trial 009, in which the 240 mg was studied, it appears that 240 mg may be more efficacious than the 120 mg dose

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Finally, the sponsor should be requested to design and perform a study to address the effects of febuxostat on the incidence of clinically important gouty flares.

## 7. Integrated Review of Safety

For a complete review of the safety database for NDA 21-856 the reader is referred to the safety review by Dr. Tatiana Oussova.

## 8. Additional Clinical Issues

### 8.1 Dosing Regimen and Administration

As discussed above, the 80 and 120 mg doses appear to be quite efficacious in lowering serum urate levels to less than 6 mg/dL and there is a dose response at least in terms of efficacy. The 240 mg dose appears to be slightly more efficacious than the 120 mg dose both for lowering of serum urate levels as well as possibly reducing the number of gouty attacks. However, there is concern with the use of the 80 and 120 mg doses in the context of the safety issues raised by Dr. Oussova in her review. It is not clear if there is a dose response for safety. It is recommended that the sponsor study the 40 mg dose (or lower doses) further for both safety and efficacy related concerns.

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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

between the genders. In addition, the difference between genders for percent decrease in serum uric acid concentrations was not clinically significant (59% in females vs. 52% in males). Therefore, no dose adjustment is needed based on gender.

#### *Race*

No specific pharmacokinetic study was conducted to investigate the effects of race.

### **8.4 Pediatrics**

Primary gout is extremely rare in the pediatric population. However, hyperuricemia can occur following treatment for leukemia, for example. The sponsor is seeking the following indication: treats hyperuricemia associated with gout. Based on this, the sponsor requested a pediatric waiver, which was granted by the Division.

### **8.5 Advisory Committee Meeting**

An Arthritis Advisory Committee meeting was held to discuss trial design issues in regards to hyperuricemia and gout. Febuxostat was not specifically discussed. However, the Committee agreed that lowering serum urate levels to less than 6 mg/dL was an appropriate therapeutic goal, and the results of trials as designed would be able to address the need to identify new therapies for hyperuricemia associated with gout.

### **8.6 Literature Review**

No literature was reviewed for this NDA.

### **8.7 Postmarketing Risk Management Plan**

The sponsor submitted the following information in regards to risk management:

#### **Goals and Objectives**

*The goal of TAP's routine, risk minimization measures will be to ensure that healthcare providers are aware of the safety profile of febuxostat which allows for proper management of patients. Through routine pharmacovigilance practices, all adverse events observed during clinical trials will be evaluated in relation to realworld experience with febuxostat. In addition, assessment of adverse events and safety laboratory tests including liver function tests will continue in ongoing clinical studies. These parallel activities will allow for continued assessment and analysis.*

concerns for an increase in CHF, and SVT, as well as a potential increase in skin and liver events (at least based on higher discontinuation rates in the febuxostat group for these last 2 issues).

## 9.2 Recommendation on Regulatory Action

The sponsor has provided substantial evidence of efficacy to support the proposed indication (management of hyperuricemia associated with gout), based on 2 phase III adequate and well controlled trials, using the defined primary endpoint of reduction in serum uric acid levels to less than 6 mg/dL. However, there are a number of safety concerns including the increase in CV thromboembolic events (predominately MIs, but also CVAs), and CHF in the febuxostat treatment group (see below for details). This increase in events is not explained by differences in baseline covariates or concomitant medication use (such as NSAIDs), during the trial. There are additional safety concerns including the occurrence of supra-ventricular tachycardias (SVTs), skin, and liver AEs and/or discontinuations in the febuxostat group compared to the allopurinol group.

The sponsor should be requested to provide additional efficacy and safety data preferably from an additional trial or trials as follows: the sponsor needs to address the issue of cardiovascular safety, and it is likely that a large outcome study will be required; the sponsor should be requested to provide additional efficacy data based on the previously defined primary outcome, for the 40 \_\_\_\_\_ (the 40 mg dose for efficacy with possibly greater safety, \_\_\_\_\_ and in addition, \_\_\_\_\_ efficacy using a clinical outcome such as gouty attacks and tophi size. Additional information on subjects with renal insufficiency should also be provided with these additional studies.

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Therefore, based on the above assessments, the risk/benefit analysis is not favorable for this drug at this time. It is recommended that an approvable action be taken based on the demonstration of efficacy but because of the ongoing safety concerns.

## 9.3 Recommendation on Postmarketing Actions

### 9.3.1 Risk Management Activity

There are no risk management recommendations at this time.

### 9.3.2 Required Phase 4 Commitments

The following are recommendations for postmarketing studies, should febuxostat ultimately be approved: study the efficacy and safety of \_\_\_\_\_ 40 mg dose (lower doses may be considered for study; the purpose of this is to identify the lowest effective dose) \_\_\_\_\_

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\_\_\_\_\_ A long term clinical study should also be performed to identify whether the number of gout flares is reduced. There are no commitments related to PREA that need to be addressed for the indication that was sought in this NDA.

### 9.3.3 Other Phase 4 Requests

It is recommended that drug interaction studies be performed with azathioprine and theophylline because it is known from allopurinol that xanthine oxidase inhibitors may interact with these drugs. Further, it is recommended that additional PK studies be performed in renally impaired subjects because this drug is likely to be used extensively in this population. A drug interaction study with warfarin should also be performed.

### 9.4 Labeling Review

The reader is referred to the line-by-line review in the appendix. \_\_\_\_\_

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### 9.5 Comments to Applicant

#### Efficacy:

1. The efficacy of the 80, 120, and 240 mg doses in terms of lowering serum urate levels is demonstrated.

#### Safety:

1. There is an increased rate of CV Thromboembolic events such as MI, stroke, TIA, and cardiac arrest, for febuxostat as compared to either allopurinol or placebo. In addition there appears to be an increase in events related to CHF, SVT and a greater number of discontinuations for skin and liver related causes in the febuxostat treatment group.

2. There is concern for the interaction of febuxostat with warfarin. There were 2 cases of retroperitoneal hemorrhage associated with the use of febuxostat in patients on warfarin.

3. There is insufficient information on the use of febuxostat in renally impaired individuals. It is not clear that no dose adjustments are necessary.

4. There is insufficient information on the co-administration of febuxostat and azathioprine or theophylline.

Information needed to resolve these issues:

1. You should evaluate further the 40 mg dose (or lower doses) for both safety and efficacy. This will involve a trial or trials sufficiently powered to adequately assess CV safety.

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3. You should evaluate the interaction with theophylline and azathioprine.

5. You should evaluate the effects of febuxostat on gouty flares and size of tophi.

6. You should evaluate the interaction of warfarin and febuxostat.

7. You should evaluate the PK of febuxostat in renally impaired individuals.

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## 10. Appendices

### 10.1 Review of Individual Study Reports

#### 10.1.1 Trial 009

##### 1. Protocol

This was a Phase 3, multicenter, randomized, double-blind, allopurinol-controlled, placebo-controlled, parallel-group, dose-response, 5-arm study designed to compare the safety and efficacy of febuxostat versus placebo and allopurinol in subjects with gout. The objective of this study was to compare the safety and efficacy of different oral doses of febuxostat versus placebo and allopurinol in subjects with gout.

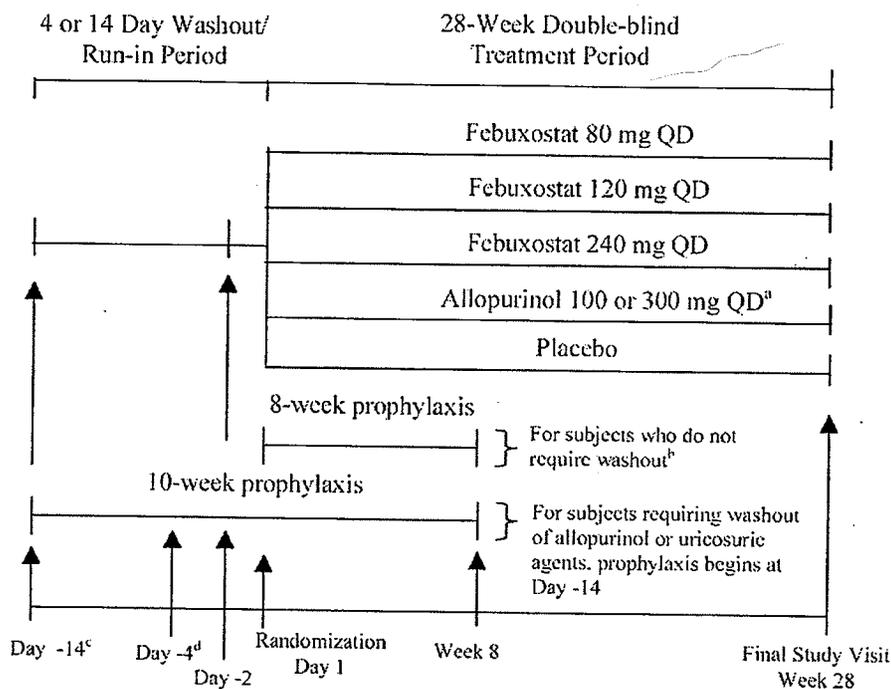
This adequate and well-controlled study was intended to be used as a Pivotal Phase 3 study to support an indication for the use of febuxostat 80 and 120 mg QD in the management of hyperuricemia in patients with gout. This study was conducted as a randomized, double-blind, multicenter, placebo-controlled, allopurinol-controlled, parallel-group design. This study design assumed an approximate 45% difference between the placebo rate and the lowest febuxostat response rate, which was felt to be a clear clinical benefit compared to placebo. In addition, the febuxostat 80 mg QD and 120 mg QD treatment groups were compared to the allopurinol 300/100 mg QD treatment group to establish the efficacy of febuxostat versus an active control. The febuxostat 240 mg QD dose was included in the study to capture safety data at twice the anticipated clinical dose of 120 mg QD. A 28-Week Double-blind Treatment Period provided longer-term efficacy and safety data while limiting subject exposure to placebo. The 14-day washout of allopurinol and uricosuric agents was sufficient to prevent any effect of any of these agents on the study endpoint.

Given the common occurrence of renal disease in this population and due to safety concerns associated with allopurinol administration, randomization was stratified by renal function. The doses and dose regimens of allopurinol 300 mg QD (for subjects randomly assigned to allopurinol who had serum creatinine  $\leq 1.5$  mg/dL on Day -2) or 100 mg QD (for subjects randomly assigned to allopurinol who had serum creatinine  $> 1.5$  mg/dL and  $< 2.0$  mg/dL on Day -2) were selected based on dosing information included in the allopurinol package insert. Also, as requested by the FDA, at least 30% of the subjects were required to have a serum urate  $> 10.0$  mg/dL.

Increased gouty attacks have been documented after onset of treatment with the XO inhibitor, allopurinol. The protocol required prophylactic treatment with naproxen or colchicine in order to minimize the risk of gout flares during the 2-week Washout/Run-in Period as well as during the first 8 weeks of the 28-Week Double-blind Treatment Period. A non-inferiority

margin of 10% and an allopurinol response rate of 60%, were discussed and agreed upon with the DAAODP in the End-of-Phase 2 meeting and in subsequent discussions and correspondence. In addition, the primary endpoint used in the study, the proportion of subjects with last three serum urate measurements <6.0 mg/dL, was also discussed and agreed upon with the DAAODP.

**Figure 2 : Schematic of trial design**



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

### Inclusion Criteria

#### Inclusion Criteria at Screening

1. Subject was 18 to 85 years of age, inclusive.

2. Females were either post-menopausal for at least 2 years, surgically sterile (including bilateral tubal ligation), or using a medically accepted means of contraception. Subjects were allowed to continue a stable regimen of at least 3 months of oral contraceptives or could have had injectable contraceptives administered within the previous 3 months. Subjects were to use an additional barrier method of birth control during the course of the study and for 30 days after the discontinuation of study drug. Subjects using a barrier method of birth control were to use an additional barrier method of birth control during the course of the study and for 30 days after the discontinuation of study drug.

3. Females were required to have a negative serum pregnancy test at Screening.

4. Subject had a history or presence of gout as defined by the preliminary criteria of the American Rheumatism Association (ARA) for the classification of the acute arthritis of primary gout.

~ the presence of characteristic urate crystals in the joint fluid and/or

~ a tophus proven to contain urate crystals by chemical or polarized light microscopic means and/or

~ the presence 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

5. Subject had normal renal function defined as:

~ a serum creatinine level  $<2.0$  mg/dL as determined by the central laboratory and

~ a creatinine clearance of  $>20$  mL/minute when creatinine clearance was calculated using the Cockcroft and Gault formula:

Estimated creatinine clearance (in mL/min):

$(140 - \text{age in years}) (\text{weight in kg}) (\text{multiply by } 0.85 \text{ for females})$

$72 (\text{serum creatinine in mg/dL})$

#### **Inclusion Criteria on Day -2**

1. Subject had a Day -2 serum urate level  $>8.0$  mg/dL, as determined by the central laboratory.

2. Subject had a Day -2 serum creatinine level  $<2.0$  mg/dL, as determined by the central laboratory.

3. Subject continued to meet all inclusion and no exclusion criteria.

## **Exclusion Criteria**

### **Exclusion Criteria at Screening**

1. Subject was breast-feeding or pregnant.
2. Subject had a history of xanthinuria.
3. Subject was intolerant of allopurinol.
  
4. Subject was receiving thiazide diuretic therapy.
5. Subject had a history of renal calculi.
6. Subject had secondary hyperuricemia.
7. Subject who required concomitant therapy with any systemic or topical medications, prescribed or nonprescribed, containing aspirin or other salicylates at the Screening Visit or during the study. Stable, low doses of aspirin were allowed (ie, <325 mg/day).
8. Subject who required >10 mg/day of prednisone during the study. Stable doses (<10 mg/day), as well as inhaled and intranasal steroids, were allowed.
9. Female subjects who had a change in hormone replacement therapy or oral contraceptive therapy within 3 months of the Screening Visit.
10. Subject whose alcohol intake was >14 drinks/week. Alcohol abuse within 5 years or current excessive alcohol use was prohibited.
11. Subject required concomitant urate-lowering therapy.
12. Subject had active liver disease or hepatic dysfunction (alanine aminotransferase [ALT] and aspartate aminotransferase [AST] both >1.5 times the upper limit of normal).
13. Subject was unable to take either gout flare medication (naproxen or colchicine) due to intolerance, hypersensitivity, active gastric ulcer disease, renal impairment and/or changes in liver enzymes.
14. Subject had any other significant medical condition as defined by the investigator that would interfere with the treatment, safety, or compliance with the protocol (eg, a clinically significant ECG result).
15. Subject had a serum urate level <8.0 mg/dL and was not taking uric acid-lowering therapy.
16. Subject had active rheumatoid arthritis and was required to take medication(s) for the treatment of his/her rheumatoid arthritis (other than prednisone  $\leq$ 10 mg/day).
17. Subject had a history of cancer (other than basal cell carcinoma of the skin) within 5 years prior to the Screening Visit, or had taken any systemic cancer chemotherapy within 5 years prior to the Screening Visit.
18. Subject who had previously participated in a clinical study in which febuxostat was administered.
19. Subject had participated in another investigational trial within the 30 days prior to the Screening Visit.

### **Removal of Subjects from Therapy or Assessment**

Participation in the study by any subject could have been terminated by the subject, the

investigator, or TAP (the sponsor) at any time during the study. Randomized subjects who prematurely discontinued from the study were not replaced.

The following procedures were to be performed for subjects who prematurely discontinued from the study: complete physical exam, ECG, weight and vital signs, Quality-of-life (QOL) questionnaires, physical assessment of tophi, chemistry, coagulation, hematology, thyroid function tests, serum pregnancy test (for female subjects), serum urate levels, blood collection for determination of febuxostat levels, microscopic urinalysis, collection of 24-hour urine if possible, concomitant medication assessment, adverse event assessment, gout flare assessment, collection of all study drug and/or prophylactic medication, and an assessment of study drug compliance.

Any study subject found to be pregnant during the Screening, Treatment, and Follow-up Periods was to be discontinued from the study and TAP was to be notified immediately.

Upon discontinuation from the study, only those procedures that would not expose the subject or the unborn child to undue risk were to be performed. Although a pregnancy was not considered an adverse event, the subject was to be followed until termination of the pregnancy or 30 days after the birth of the child. Data regarding the pregnancy and outcome of the pregnancy were to be documented on the TAP pregnancy worksheet.

#### Identity of Investigational Product(s)

Febuxostat was supplied as tablets containing 40 mg febuxostat, 80 mg febuxostat, and placebo (1 to match each dose).

Allopurinol \_\_\_\_\_, 100 mg and 300 mg tablets were manufactured by \_\_\_\_\_ for this study in their marketed container. Each allopurinol tablet was overencapsulated in an iron gray opaque (No. 00) gelatin capsule along with a \_\_\_\_\_ filler. Placebo capsules contained \_\_\_\_\_ filler in an iron gray opaque (No. 00) gelatin capsule.

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None of the clinical supplies were used past their expiration date.

Dissolution profiles for the overencapsulated (blinded) allopurinol were compared to those of the unblinded allopurinol tablets, and stability studies were conducted for matching placebo. For the blinded allopurinol capsules, the dissolution profiles were compared to the allopurinol tablet profiles. Dissolution profiles for all blinded products were similar to those of unblinded products for allopurinol. Stability studies were conducted to ensure that assay and dissolution profiles of the overencapsulated products did not change over the duration of the clinical study.

*Reviewers comments: The effect size of allopurinol used in the pivotal trials was lower than expected. The sponsor originally proposed that about 60% of subjects would have a serum uric acid less than 6 on the last 3 visits. In both phase 3 trials the result was closer to 20%. This was a concern because the sponsor wished to make comparisons of febuxostat to allopurinol. Therefore, allopurinol samples were obtained by the biopharmaceutics group to assess its activity. NEED MORE HERE*

### **Method of Assigning Subjects to Treatment Groups**

\_\_\_\_\_ provided an IVRS for the study. Sites called the system to randomize a subject to a treatment group on Day 1 and to receive subsequent study drug carton and bottle assignments. Each site was provided with instructions and training on the use of this system. Subjects were categorized as non-renal impaired (Day -2 serum creatinine >1.5 mg/dL) or moderately renal impaired (Day -2 serum creatinine >1.5 mg/dL and <2.0 mg/dL). b(4)

These 2 groups of subjects were randomly assigned separately by the IVRS based on randomization schedules provided by TAP so that treatment groups were balanced with respect to baseline renal function. Subjects with moderate renal impairment who were randomly assigned to allopurinol were assigned by the IVRS based on randomization schedules provided by TAP to receive allopurinol 100 mg QD. Subjects without renal impairment who were randomly assigned to allopurinol were assigned by the IVRS to receive allopurinol 300 mg QD. Non-renal impaired subjects were assigned sequential subject numbers beginning with 4001 and moderately renal impaired subjects were assigned sequential subject numbers beginning with 6001.

Double-blind study drug, once assigned, was not reassigned to another subject. If a subject discontinued from the study after randomization, the used or unused study drug cartons, blister cards, and bottles were to be returned to \_\_\_\_\_ for destruction. b(4)

### **Blinding**

The randomization schedule was computer-generated by the TAP Statistics Department. The randomization code was maintained in a locked, confidential location until the time of unblinding by a TAP statistician.

The study drug assignment for each subject was available to the investigator via a scratch-off label located on the study drug carton and bottle on the portion of the label that was retained by the site (for placement on the CRF) prior to dispensing the study drug to the subject. The blind could have been accessed via the scratch-off label if, in the opinion of the investigator, it was in the subject's best interest for the physician to know the study drug assignment. The investigator was to notify the sponsor before breaking the blind, unless identification of the study drug was required for emergency therapeutic measures. In the latter case, the sponsor was to be notified within 24 hours of the blind being broken. The date, time, and reason that the blind was broken were to be recorded on the appropriate CRF.

### **Prior and Concomitant Therapy**

Information regarding medications taken by the subject within 30 days prior to the Screening Visit and throughout the study was collected and recorded on the Prior/Concomitant Medications or Gout Medications CRF. This information included the name of the medication, dosage information (including frequency and route of administration), dates taken, reason for use, and stop date, if available.

Subjects were to refrain from taking any medication that was not part of the study design and could affect serum urate levels. Subjects who had taken any of the excluded medications listed below prior to the study could have been entered into the study if the excluded medication was discontinued a minimum of 5 half-lives prior to the Day 1 Visit. Allopurinol and uricosuric agents were discontinued at least 14 days prior to the Day 1 Visit.

The following medications were not to be taken during the study: commercially-obtained allopurinol (Zyloprim/Lopurin), thiazide diuretics, azathioprine, meclofenamate, mercaptopurine, chronic use of NSAIDs (other than protocol-required prophylactic therapy), salicylate-containing medications (eg, Alka-Seltzer) other than low-dose aspirin (<325 mg/day), trimethoprim-sulfamethoxazole (eg, Bactrim and Septra), uricosuric agents and combinations (eg, probenecid [Benemid], colchicine probenecid [ColBenemid], and sulfapyrazone [Anturane]), benzbromarone, losartan potassium (Cozaar), valsartan/hydrochlorothiazide (Diovan HCT), cyclophosphamide, pyrazinamide, methotrexate, intravenous colchicine, and prednisone >10 mg/day. Subjects were allowed to take the following medications during the study, but they must have been at stable, low doses: ascorbic acid (ie, <500 mg/day), low-dose aspirin (ie, <325 mg/day), citrate (<500 mg/day), nicotinic acid, and prednisone (<10 mg/day). The following medications were allowed on an as needed basis only: acetaminophen, non-salicylate NSAIDs, and glyceryl guaiacolate.

*Reviewers comments: Prohibited medication list appears to be appropriate as these drugs can either affect serum uric acid or can potentially alter the development of clinical gout.*

### **Treatment Compliance**

Subjects returned the previously dispensed cartons (including the blister cards) and bottles of study drug at each visit, except at Week 2 and Week 6, so that subject compliance could be monitored. Compliance was assessed by pill counts (large tablets, small tablets, and capsules) at each study visit during the 28-Week Double-blind Treatment Period except Week 2 and Week 6.

The following tables summarize the treatment period and followup studies.

**Table 25 : treatment and followup studies**

Clinical Review  
 {Schiffenbauer, Joel}  
 {NDA 21-856}  
 {Uloric/febuxostat}

PROCEDURE	Washout/Run-in Period			28-Week Double-blind Treatment Period												
	Screening Day -14 Visit 1	Day -4 <sup>1</sup> Visit 2	Day -2 Visit 3	Day 1 Visit 4	Week 2 Visit 5	Week 4 Visit 6	Week 6 Visit 7	Week 8 Visit 8	Week 12 Visit 9	Week 16 Visit 10	Week 20 Visit 11	Week 24 Visit 12	Week 28 <sup>1</sup> Visit 13			
<b>Non-laboratory procedures</b>																
Informed consent	X															
Medical history (including medications), social history, and height	X															
Grant history	X															
Complete physical exam			X						X				X			
Brief physical exam	X			X		X		X		X	X	X				
12-lead ECG			X <sup>1</sup>										X <sup>2</sup>			
Weight and vitals	X		X	X		X		X	X	X	X	X	X			
Quality-of-Life Questionnaires <sup>3</sup>				X									X			
Tophus physical assessment	X			X		X		X	X	X	X	X	X			
AE-Rash Assessment		X	X	X	X	X	X	X	X	X	X	X	X			
Grant flare assessment (if applicable)	X	X	X	X	X	X	X	X	X	X	X	X	X			
Concomitant med assessment	X	X	X	X	X	X	X	X	X	X	X	X	X			
Site contacts the IVRS	X			X	X	X	X	X	X	X	X	X	X			
Dispense naproxen or celecoxib <sup>4</sup>	X			X		X										

- For subjects who required washout of allopurinol or uricosuric agents prior to the study, the Screening Visit occurred on Day -14. For subjects who did not require washout of allopurinol or uricosuric agents, the Screening Visit occurred on Day -4.
- For subjects who did not require washout of allopurinol or uricosuric agents prior to the study, the Screening Visit occurred on Day -4, in lieu of this visit. All other subjects had a Day -4 Visit.
- Or at premature discontinuation.
- Subjects who were not enrolled at sites doing the PK/PD substudy had 1 ECG performed during this visit using the site's equipment (a copy of this ECG was sent to the central ECG reader). Subjects who were enrolled at sites doing the PK/PD substudy had 3 ECGs performed (15 minutes apart) during this visit using standardized equipment provided by [REDACTED].
- Subjects who were not enrolled at sites doing the PK/PD substudy had 1 ECG performed during this visit, using the site's equipment (a copy of this ECG was sent to the central ECG reader). Subjects who were enrolled at sites doing the PK/PD substudy had 1 ECG performed during this visit using standardized equipment provided by [REDACTED].
- All subjects completed the SF-36<sup>SM</sup> Health Survey and the Grant Assessment Questionnaire during these visits. Subjects with a history of congestive heart failure at the Screening Visit also completed the Minnesota Living with Heart Failure<sup>SM</sup> Questionnaire during these visits.
- For those subjects with palpable tophi present.
- Subjects who were taking allopurinol or uricosuric agents prior to study were dispensed naproxen or celecoxib at the Day -14 and Week 4 Visits. Subjects who were not receiving allopurinol or uricosuric agents prior to study were dispensed naproxen or celecoxib at the Day 1 and Week 4 Visits.

b(4)

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PROCEDURE	Washout/Run-in Period			28-Week Double-blind Treatment Period												
	Screening Day -14 Visit 1	Day -4 <sup>1</sup> Visit 2	Day -2 Visit 3	Day 1 Visit 4	Week 2 Visit 5	Week 4 Visit 6	Week 6 Visit 7	Week 8 Visit 8	Week 12 Visit 9	Week 16 Visit 10	Week 20 Visit 11	Week 24 Visit 12	Week 28 <sup>1</sup> Visit 13			
Collect unused naproxen or celecoxib						X		X								
Prophylaxis medication compliance				X		X		X								
Subject randomized				X												
Dispense study drug				X		X		X	X	X	X	X				
Collect unused study drug						X		X	X	X	X	X	X			
Telephone call to subject to discuss study drug dosing										X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>	X <sup>2</sup>			
Study drug compliance					X	X	X	X	X	X	X	X	X			
Discuss open-label extension study													X			
<b>Blood Tests</b>																
Chemistry labs <sup>10</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X			
Serum urate levels <sup>11</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X			
Coagulation <sup>12</sup>	X			X				X					X			
Hematology labs <sup>13</sup>	X			X		X		X	X	X	X	X	X			
Thyroid function tests <sup>14</sup>	X			X									X			
Serum pregnancy test <sup>15</sup>	X		X						X				X			
Febuxostat trough concentrations <sup>16</sup>										X		X	X			

- For subjects who required washout of allopurinol or uricosuric agents prior to the study, the Screening Visit occurred on Day -14. For subjects who did not require washout of allopurinol or uricosuric agents, the Screening Visit occurred on Day -4.
- For subjects who did not require washout of allopurinol or uricosuric agents prior to the study, the Screening Visit occurred on Day -4, in lieu of this visit. All other subjects had a Day -4 Visit.
- Or at premature discontinuation.
- Three days prior to the Week 16, 20, 24, and 28 Visits, the coordinator called the study subject to remind them that the double-blind study drugs were to be taken on the 2 days prior to the visit, but not on the morning of the visit.
- Chemistry tests included glucose, total cholesterol, triglycerides, total protein, albumin, total bilirubin, amylase, serum glutamic oxaloacetic transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), blood urea nitrogen (BUN), creatinine, magnesium, sodium, potassium, chloride, bicarbonate, phosphorus, and calcium.
- Serum urate levels were blinded to the subject, investigator and staff, and Sponsor beginning on Day 1.
- Coagulation tests included prothrombin time (PT) and partial thromboplastin time (PTT).
- Hematology tests included red blood cell (RBC) count, white blood cell (WBC) count, total and differential, platelet count, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and reticulocyte count.
- Thyroid tests included thyrotrophic hormone (TSH), triiodothyronine (T<sub>3</sub>), thyroxine (T<sub>4</sub>), and free T<sub>4</sub>.
- A serum pregnancy test was performed at the Screening (Day -14 or Day -4), Day -2, Week 12 and Week 28 Visits for female subjects of child-bearing potential. In addition, all other female subjects participating in the study were to have a serum pregnancy test performed at the Screening Visit (Day -14 or Day -4) and at the End of Study Visit (Week 28).
- Podose sample was collected at these visits for all study subjects.

Clinical Review  
 {Schiffenbauer, Joel}  
 {NDA 21-856}  
 {Uloric/febuxostat}

PROCEDURE	Washout/Run-in Period			28-Week Double-blind Treatment Period									
	Screening <sup>1</sup> Day -14 Visit 1	Day -4 <sup>2</sup> Visit 2	Day -2 Visit 3	Day 1 Visit 4	Week 2 Visit 5	Week 4 Visit 6	Week 6 Visit 7	Week 8 Visit 8	Week 12 Visit 9	Week 16 Visit 10	Week 20 Visit 11	Week 24 Visit 12	Week 28 <sup>3</sup> Visit 13
<b>Urine tests</b>													
Urinalysis with microscopy <sup>17</sup>	X			X		X		X	X	X	X	X	X
Urine pregnancy test <sup>18</sup>				X									
Distribution of 24-hour urine collection container <sup>19</sup>			X									X	
24-hour urine collection				X									X
<b>Population PK/PD substudy-specific procedures<sup>20</sup></b>													
0.25-hour postdose blood collection <sup>21</sup>										X		X	
0.75-2.0-hour postdose blood collections, vital signs, and ECG <sup>22</sup>										Occurred on a PK/PD Substudy Visit day between the Week 16 and Week 28 Visits			
2.5-4.0-hour postdose blood collections, vital signs, and ECG <sup>22</sup>													
5.0-12.0-hour postdose blood collection <sup>23</sup>													

- 1 For subjects who required washout of allopurinol or uricosuric agents prior to the study, the Screening Visit occurred on Day -14. For subjects who did not require washout of allopurinol or uricosuric agents, the Screening Visit occurred on Day -4.
- 2 For subjects who did not require washout of allopurinol or uricosuric agents prior to the study, the Screening Visit occurred on Day -4, in lieu of this visit. All other subjects had a Day -4 Visit.
- 3 Or at premature discontinuation.
- 17 Urinalysis included a determination of color, bilirubin, urobilinogen, leukocyte esterase, specific gravity, pH, protein, blood, ketones, nitrite, glucose, and a microscopic evaluation for WBCs, RBCs, casts, epithelial cells, yeast, bacteria and crystals. Repeat urinalysis was to be obtained within 1 week for blood-positive (+) result. If retest was also +, the investigator was to contact the TAP monitor to discuss further evaluation.
- 18 A Day 1 urine pregnancy test was required for all female subjects.
- 19 Subjects received a collection container at their Day -2 Visit for the 24-hour collection to start on Day -1 and at their Week 24 Visit for the collection to start the day before the Week 28 Visit.
- 20 Only for sites participating in the PK/PD substudy.
- 21 At the Week 16 or 24 Visit (but not both). 1 population PK/PD and 1 serum urate sample were collected 15 minutes postdose.
- 22 An ECG was performed using standardized equipment provided by [REDACTED] within 15 minutes of the postdose blood population PK/PD and serum urate blood sample collections. Vital signs were also recorded.
- 23 1 population PK/PD and 1 serum urate sample were collected 5.0-12.0 hours postdose.

**Efficacy Variable(s)**

**Primary Variable(s)**

The primary efficacy variable was the proportion of subjects whose last 3 serum urate levels were <6.0 mg/dL.

**Secondary Variable(s)**

The following secondary efficacy variables were assessed:

1. The proportion of subjects whose serum urate levels were <6.0 mg/dL.
2. The percent reduction in serum urate levels.
3. The percent reduction in primary tophus size, as determined by physical measurement in the subset of subjects with a primary palpable tophus at the Screening Visit.
4. The reduction in the total number of tophi in the subset of subjects with palpable tophi at the Screening Visit.
5. The proportion of subjects requiring treatment for a gout flare between Weeks 8 and 28 of the 28-Week Double-blind Treatment Period.

**Data Sets Analyzed**

All primary and secondary efficacy analyses were performed on the intent-to-treat (ITT) population, except for the secondary efficacy analyses for the percent reduction in primary tophus size and the reduction in the total number of tophi. The ITT population

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b(4)

was defined as all randomized subjects who received at least 1 dose of study drug and had serum urate levels  $\geq 8.0$  mg/dL at the last visit prior to Day 1 as determined by the central laboratory.

The analysis for the percent reduction in primary tophus size was performed on the subset of ITT subjects with a primary palpable tophus at baseline. The analysis for the reduction in the total number of tophi was performed on the subset of ITT subjects with palpable tophi at baseline. The last tophus examination obtained prior to the first dose of study drug on Day 1 was used to determine a subject's inclusion in these populations, as well as the baseline primary tophus size and baseline total number of tophi. All randomized subjects who received at least 1 dose of study drug were included in the safety analyses.

### **Primary Efficacy Variable**

The primary efficacy variable was the proportion of subjects whose last 3 serum urate levels were  $< 6.0$  mg/dL. After applying the visit windows, each subject's last 3 serum urate levels, regardless of the subject's study completion status, were used to determine the subject's response for the primary efficacy variable. In order to be considered a responder, each of the last 3 serum urate levels must have been  $< 6.0$  mg/dL. If a subject prematurely discontinued from the study before at least 3 serum urate levels were obtained, the subject was considered a nonresponder.

The treatment groups were compared in the following sequential order:

1. Each febuxostat treatment group was compared to the placebo group with a CMH test stratified by baseline renal function. Superiority of a febuxostat treatment group to the placebo group was declared if the p-value from the CMH test was less than or equal to the critical significance level based on Hochberg's method.<sup>38</sup> If each dose of febuxostat was shown to be superior to placebo, the procedure proceeded to step 2.
2. Binomial 97.5% confidence intervals, based on the normal approximation for the binomial distribution, were calculated for the differences in response rates between each treatment group of febuxostat (80 mg QD and 120 mg QD) and the allopurinol 300/100 mg QD treatment group. Non-inferiority to allopurinol was declared if the absolute value of the lower bound of the 97.5% confidence interval did not exceed 10%.
3. Each febuxostat treatment group that was shown to be non-inferior to allopurinol in step 2 was compared to the allopurinol 300/100 mg QD treatment group to test for superiority. The test for superiority was performed using a CMH test stratified by baseline renal function. If both treatment groups of febuxostat were compared to allopurinol, superiority of a febuxostat treatment group to the allopurinol 300/100 mg QD treatment group was declared if the p-value from the CMH test was less than or equal to the critical significance level based on Hochberg's method and the response rate for the febuxostat treatment group was higher than that for the allopurinol 300/100 mg QD treatment group. If only 1 treatment group

of febuxostat was compared to allopurinol, superiority of the febuxostat treatment group to the allopurinol 300/100 mg QD treatment group was declared if the p-value from the CMH test was  $<0.05$ .

In the Hochberg's method in steps 1 and 3, the p-values from the pairwise comparisons were ordered from smallest to largest. The largest p-value was compared to 0.05. If the largest p-value was less than or equal to 0.05, all the comparisons were considered statistically significant. If the largest p-value was greater than 0.05, then the comparison corresponding to that p-value was not considered statistically significant. The second largest p-value was then compared to  $0.05/2=0.025$ . If the second largest p-value was less than or equal to 0.025, then all the remaining comparisons were considered statistically significant. If the second largest p-value was greater than 0.025, then the comparison corresponding to that p-value was not considered statistically significant. The third largest p-value was then compared to  $0.05/3=0.017$  (only in step 1 if applicable) and if it was less than or equal to 0.017, the corresponding comparison was considered statistically significant.

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

A sensitivity analysis was conducted for the primary efficacy variable by using the available (1 or 2) serum urate levels to determine response for subjects who prematurely discontinued before at least 3 serum urate levels were obtained. This analysis examined the effect of assigning these subjects as nonresponders in the primary analysis. Subjects without post-baseline serum urate levels were not included in this analysis.

Analyses for the proportion of subjects whose last 3 serum urate levels were  $<6.0$  mg/dl were conducted by age ( $<45$ , 45 to  $<65$ ,  $>65$  years), gender (male, female), race (Caucasian, non-Caucasian), baseline BMI ( $<18.5$ , 18.5 to  $<25$ , 25 to  $<30$ ,  $>30$  kg/m<sup>2</sup>), alcohol use (drinkers, non-/ex-drinkers), overall compliance ( $<80\%$ , 80 to  $<90\%$ ,  $>90\%$ ), baseline serum creatinine ( $<1.5$  mg/dL,  $>1.5$  mg/dL), baseline measured creatinine clearance ( $>50$  mL/min/1.73 m<sup>2</sup>,  $<50$  mL/min/1.73 m<sup>2</sup>), baseline serum urate levels ( $<9.0$ , 9.0 to  $<10.0$ ,  $>10.0$  mg/dL), use of previous urate-lowering therapy (prior use, no prior use), baseline palpable tophus presence (tophus present, tophus absent), history of cardiovascular risk factors ( $\geq 1$  risk factor, no risk factors), use of low-dose aspirin (use, no use), tobacco use (tobacco user, non-/ex-tobacco user), and metabolic syndrome (subjects with syndrome, subjects without syndrome). Pairwise comparisons between the treatment groups were made with a CMH test adjusting for each factor.

A subject was categorized as having at least 1 cardiovascular risk factor if he had a history of cardiovascular disease, diabetes, hypercholesterolemia, hyperlipidemia, or hypertension.

### Secondary Efficacy Variables

The following secondary efficacy variables were assessed:

1. The proportion of subjects whose serum urate levels were <6.0 mg/dL.
2. The percent reduction in serum urate levels.
3. The percent reduction in primary tophus size, as determined by physical measurement in the subset of subjects with a primary palpable tophus at the Screening Visit.
4. The reduction in the total number of tophi in the subset of subjects with palpable tophus at the Screening Visit.
5. The proportion of subjects requiring treatment for a gout flare between Weeks 8 and 28 of the 28-Week Double-blind Treatment Period.

Pairwise comparisons for the secondary efficacy variables were made between the treatment groups. No adjustments for multiple comparisons were performed.

#### **Determination of Sample Size**

A total of 1000 subjects (125 subjects in each of the placebo and febuxostat 240 mg QD treatment groups and 250 subjects in each of the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups) were planned to be enrolled into this study. This sample size, based on the assumptions stated below, was to provide: 1) at least 95% power to detect a difference of at least 45% between each of the febuxostat treatment groups and placebo for the primary efficacy variable; 2) at least 80% power to meet the non-inferiority criteria between at least 1 febuxostat treatment group and the allopurinol 300/100 mg QD treatment group for the primary efficacy variable; and 3) at least 90% power to detect a 15% difference between a febuxostat treatment group and the allopurinol 300/100 mg QD treatment group for the primary efficacy variable.

A larger number of subjects was required to show non-inferiority between the febuxostat 80 mg QD and 120 mg QD treatment groups and the allopurinol 300/100 mg QD treatment group than was required to detect a difference between the placebo treatment group and the febuxostat treatment groups. Since the febuxostat 240 mg QD treatment group was included in this study to establish the safety profile of a dose that was twice the anticipated maximum clinical dose of 120 mg QD, comparisons between the febuxostat 240 mg QD treatment group and the allopurinol treatment group were not powered. Therefore, an unequal randomization was chosen for this study in which subjects were randomly assigned in a 1:2:2:1:2 ratio to receive placebo, febuxostat 80 mg QD, febuxostat 120 mg QD, febuxostat 240 mg QD, or allopurinol. For the determination of non-inferiority between each of the febuxostat treatment groups (80 mg QD and 120 mg QD) and the allopurinol treatment group, the sample size calculation assumed a true response rate of 60% for the allopurinol treatment group and at least 64% for the febuxostat treatment groups, which was based on the TMX-00-004 data and a literature review of historical allopurinol data and in consideration of the differences in expected response rates between the Phase 2 and 3 endpoints. In Study TMX-00-004, a Phase 2, dose-response study in subjects with gout, the proportions of subjects with a serum urate level <6.0 mg/dL after 4 weeks of treatment were 0%, 56%, 76%, and 94% for the placebo, febuxostat 40 mg QD, febuxostat 80 mg QD, and febuxostat 120 mg QD treatment groups, respectively.

## 2. Amendments

### Changes in the Conduct of the Study or Planned Analyses Protocol Changes

There were 3 amendments to the original protocol.

#### **Amendment No. 1, dated 30 January 2003:**

The primary purpose of Amendment No. 1 was to update Section 8.0, Statistical Methods and Determination of Sample Size, and Section 9.0, Discussion and Justification of Study Design of the protocol. These sections were updated to reflect a change in the primary efficacy variable for the study based on the End-of-Phase 2 discussions with the DAAODP.

The primary efficacy variable for this study was changed to the proportion of subjects whose last 3 serum urate levels were <6.0 mg/dL. The original endpoint had been the proportion of subjects whose serum urate levels decreased to <6.0 mg/dL after 28 weeks of treatment.

The comparisons between treatment groups were also clarified. Comparisons of febuxostat to allopurinol to test for non-inferiority were only performed if the observed response rate for allopurinol was at least 60% and used a non-inferiority criterion of 10%.

#### **Amendment No. 2, dated 11 March 2003:**

The primary purpose of Amendment No. 2 was to:

- Clarify that a minimum of 30% of the subjects enrolled into the study were to have a Day -2 serum urate value >10.0 mg/dL.
- Add the performance of 6 ECGs to the PK/PD substudy (using standardized equipment and digital transmission of data to \_\_\_\_\_, in place of the previously required 2 ECGs (using nonstandardized equipment and no digital transmission of data).
- Specify that copies of the tracings for ECGs performed at non-PK/PD substudy sites were to be sent to a central ECG reader for interpretation.

b(4)

#### **Amendment No. 3, dated 12 February 2004:**

The primary purpose of Amendment No. 3 was to update Section 8.1.3 of the statistical methods such that the closed testing procedure for the comparisons for the primary efficacy variable would be consistent between the 2 febuxostat pivotal trials (Studies C02-009 and C02-010). Section 9.4, Selection of Doses in the Study was updated to clarify the expected response rate for allopurinol in the study and how this response rate was determined. In addition, references to the Canadian study sites were removed, as only US sites were used in this trial.

### **Statistical Methods Changes**

The following changes were made to the planned statistical analyses to provide a more complete set of analyses. In general, these changes were done after the blind was broken to clarify the results and to add additional exploratory analyses. The data collection window was clarified to state that all laboratory and vital signs data collected within 1 day of the final dose would be used in the safety analyses. The definition of the "Final Visit" was clarified to state that each subject's last post-baseline visit would be used in the analyses (ie, the baseline value would not be used as the "Final Visit"). The treatment assignment for misrandomized subjects was clarified to state that the actual treatment received on Day 1 would be considered the treatment group for known cases.

The timing of premature discontinuations was added to the summary of subject disposition for completeness. The number of subjects included in the PK/PD substudy also was summarized. Summary statistics were generated for the PK/PD substudy using all subjects instead of all ITT subjects to include more data in the summary. Separate summaries were generated for concomitant gout medications taken at any time and taken during a gout flare to further characterize concomitant gout medication usage.

Additional analyses for the primary efficacy variable were conducted by adjusting for low-dose aspirin use, tobacco use, and metabolic syndrome to further investigate possible explanatory factors. Demographic summaries were also added for these factors as necessary. The overall compliance subgroups were revised since few subjects had overall compliance <80%.

The analysis subset for the secondary efficacy variable of percent change in primary tophus size was redefined to use subjects with a primary palpable tophus at the Screening Visit instead of subjects with palpable tophi at the Screening Visit since a primary tophus could not be identified for some subjects with palpable tophi at the Screening Visit.

The number and percentage of subjects whose serum urate levels were <6.0 mg/dL at the Final Visit were summarized by treatment group and baseline serum urate level to further examine the effect of baseline serum urate level. An analysis of subjects requiring treatment for a monoarticular or polyarticular gout flare was added to explore the treatment effect on flares in multiple joints. Additional pairwise comparisons were performed for the percentage of subjects requiring treatment for a gout flare at the last time period (Week 24 to 28). An additional analysis was conducted for the percent change in primary tophus size after excluding elbow tophi to evaluate the influence of elbow measurements on the overall results.

Additional summaries for the percent change in primary tophus size and percentage of subjects requiring treatment for a gout flare were conducted for subjects with an average post-baseline serum urate level <6.0 mg/dL or  $\geq$ 6.0 mg/dL to examine the effect of serum urate reduction on these variables.

Additionally, adverse events were summarized by baseline serum creatinine (<1.5 mg/dL, >1.5 mg/dL) to further define the safety profile.

Analysis of ECG quantitative data was performed only for subjects in the PK/PD substudy since quantitative data were not collected for all enrolled subjects. Bazette's corrected QT interval was added to the ECG quantitative analysis.

Additional safety analyses were conducted for subjects with potentially concerning vital signs and subjects with treatment-emergent ECG findings. Some electrocardiogram readings were analyzed centrally by \_\_\_\_\_ in addition to \_\_\_\_\_. Significant treatment-emergent findings from either central reader were included in the summary of MedDRA-coded results.

b(4)

SAS for Unix was used instead of SAS for Windows in all analyses.

### 3. Post Hoc changes

None were noted.

### 4. Results

#### 4.1 Disposition

#### **Disposition of Subjects**

One thousand seventy-two subjects were randomized in the study in the US and received at least 1 dose of study drug. 134 subjects received placebo, 267 received febuxostat 80 mg QD, 269 received febuxostat 120 mg QD, 134 received febuxostat 240 mg QD, and 268 received allopurinol 300/100 mg QD. Results from subjects receiving either allopurinol 100 mg QD (n=10) or 300 mg QD (n=258) were summarized together in all statistical tables.

A clinical site closure due to GCP noncompliance occurred at site 18032 (Dr. \_\_\_\_\_). A letter regarding this closure was submitted to the FDA on 12 May 2004, which indicated that the data for the 2 subjects enrolled at the site [4115 (febuxostat 80 mg QD) and 4123 (allopurinol 300 mg QD)] would be excluded from the clinical trial database. Review of the data revealed that both were non-responders in the primary efficacy analysis and neither of these subjects experienced adverse events or gout flares.

b(4)

Objective laboratory data were available for these subjects, therefore a decision was made upon consultation with the FDA to include these data in the database for efficacy and safety analyses.

**Table 26 : Disposition of subjects**

	Placebo	Febuxostat 80 mg QD	Febuxostat 120 mg QD	Febuxostat 240 mg QD	Allopurinol 300/100 mg QD	All Subjects
All Randomized Subjects	134	267	269	134	268	1072
	n (%)					
Completed Study	101 (75%)	174 (65%)	200 (74%)	86 (64%)	211 (79%)	772 (72%)
Prematurely Discontinued	33 (25%)	93 (35%)	69 (26%)	48 (36%)	57 (21%)	300 (28%)
Timing of Premature Discontinuations (weeks) <sup>a</sup>						
<4	12 (36%)	20 (22%)	14 (20%)	15 (31%)	19 (33%)	80 (27%)
4 to <8	3 (9%)	18 (19%)	13 (19%)	13 (27%)	9 (16%)	56 (19%)
8 to <12	7 (21%)	16 (17%)	13 (19%)	5 (10%)	11 (19%)	52 (17%)
12 to <20	8 (24%)	25 (27%)	20 (29%)	10 (21%)	12 (21%)	75 (25%)
20 to <28	3 (9%)	14 (15%)	7 (10%)	5 (10%)	5 (9%)	34 (11%)
≥28	0	0	2 (3%)	0	1 (2%)	3 (1%)
Primary Reason <sup>a</sup> :						
Lost to follow-up	10 (30%)	19 (20%)	17 (25%)	9 (19%)	17 (30%)	72 (24%)
Adverse events	5 (15%)	18 (19%)	16 (23%)	11 (23%)	18 (32%)	68 (23%)
Personal reason(s)	9 (27%)	16 (17%)	16 (23%)	9 (19%)	9 (16%)	59 (20%)
Other	3 (9%)	15 (16%)	8 (12%)	6 (13%)	5 (9%)	37 (12%)
Gout flare	0	13 (14%)	6 (9%)	8 (17%)	1 (2%)	28 (9%)
Protocol violation	3 (9%)	6 (6%)	3 (4%)	3 (6%)	6 (11%)	21 (7%)
Therapeutic failure	3 (9%)	6 (6%)	3 (4%)	2 (4%)	1 (2%)	15 (5%)

a Denominator is the number of subjects who prematurely discontinued from each group.  
 Cross-reference: Statistical Tables 14.1.1 and 14.1.2.1 and Appendix 16.2-1.1

*Reviewers comments: There were fewer subjects who prematurely discontinued in the allopurinol group. This appears to be due, at least in part, to the fact that more subjects in the febuxostat treated groups discontinued due to gout flares. In addition there were somewhat more protocol violators in the allopurinol treated group. However, because a responder analysis was used for the primary efficacy outcome, these findings likely did not have an adverse impact on the validity of the study results.*

### Protocol Deviations

Protocol deviations in this study included deviations due to violations in admission criteria, administration of the incorrect treatment, use of prohibited concomitant medications, and several other miscellaneous violations.

A total of 89 subjects (11 placebo, 26 febuxostat 80 mg QD, 22 febuxostat 120 mg QD, 11 febuxostat 240 mg QD, and 19 allopurinol 300/100 mg QD) had deviations from the admission criteria for the study (Appendix 16.2-2.1). Nine subjects (1 placebo [4044], 3 febuxostat 80 mg QD [4326, 4673, and 4855], 2 febuxostat 120 mg QD [4251 and 4580], 1 febuxostat 240 mg QD [4948], and 2 allopurinol 300/100 mg QD [4119 and 4125]) were prematurely discontinued, at the request of TAP, due to admission criteria violations.

The most admission criteria violations were associated with subjects being enrolled with a history of renal calculi (17 subjects: 3 placebo, 3 febuxostat 80 mg QD, 3 febuxostat 120 mg QD, 2 febuxostat 240 mg QD, and 6 allopurinol 300/100 mg QD). Two of these subjects (4218 and 4095) were approved by TAP to enter the study. Subject 4218 reported a renal calculus in 1974 with no gout treatment for 19 years. He was subsequently treated with allopurinol with no further episodes of calculi. Subject 4095 had a kidney stone at age 13 during a 4-month hospitalization. These subjects had no recurrence of renal calculi during the study. The investigator discontinued 12 of the remaining subjects after inadvertently enrolling them in the study with a history of renal calculi. Two additional subjects (4175 and 4630) completed the study without experiencing any renal calculi. Subject 4183 was lost to follow-up after Visit 10; no renal calculi were reported.

Fifteen admission criteria violations were due to subjects with concomitant thiazide diuretic therapy (3 placebo, 3 febuxostat 80 mg QD, 3 febuxostat 120 mg QD, 4 febuxostat 240 mg QD, and 2 allopurinol 300/100 mg QD). Two subjects (4422 and 4975) were appropriately washed off the medication prior to randomization. One subject (4681) discontinued the thiazide on Day 1 of the study. Two subjects (4459 and 4948) were prematurely discontinued from the study due to taking the prohibited medication. Five subjects (4141, 4485, 4568, 4914, and 6037) stopped thiazide medication during the course of the study and continued in the study. For 1 subject (4058) thiazide use was not noted until the subject had 3 weeks of study participation remaining; the subject was allowed to continue thiazide. For the remaining subjects, the site overlooked the use of thiazide medications, and the subjects used their prescribed thiazide medication for the duration of their study participation .

Fifteen admission criteria violations were associated with subjects whose alcohol intake was  $\geq 14$  drinks/week (5 febuxostat 80 mg QD, 4 febuxostat 120 mg QD, 3 febuxostat 240 mg QD, and 3 allopurinol 300/100 mg QD). For 3 subjects (4258, 4593, and 4920), TAP was consulted prior to randomization. For the remaining subjects, TAP was notified after randomization. In all cases where TAP was consulted, subjects were to be instructed by the site to drink less than 14 drinks/week.

A total of 12 subjects had active liver disease or hepatic dysfunction at the Screening Visit, as defined by an ALT and AST  $>1.5$  times the upper limit of normal (2 placebo, 2 febuxostat 80 mg QD, 5 febuxostat 120 mg QD, and 3 allopurinol 300/100 mg QD); 6 subjects (4226, 4257, 4567, 4644, 4498, and 4654) had acceptable labs prior to randomization. All except 2 subjects (4226 and 4637) completed the study. Subject 4226 prematurely discontinued due to decreased libido. Subject 4637 experienced an increase in liver function values after randomization and was prematurely discontinued after Visit 5 due to worsening of elevated liver function tests.

Eight subjects had abnormal renal function (1 placebo, 3 febuxostat 80 mg QD, 1 febuxostat 120 mg QD, and 3 allopurinol 300/100 mg QD). Six subjects (6009, 6021, 6028, 6038, 6039, and 6040) had their renal function assessed by 24-hour creatinine clearance prior to randomization. All measured clearances were  $>27$  mL/min/1.73 m<sup>2</sup>.

For 1 subject (6029) the estimated creatinine clearance prior to randomization was 63 mL/min. Subject 4455 had a serum creatinine < 2.0; the deviation was reported because the estimated clearance was not available prior to randomization due to the site using the wrong lab kit at the Screening Visit. For 2 of the subjects (6021 and 6028), an additional deviation was reported for a serum creatinine >2.0 mg/dL on Day -2. This deviation was also reported for Subject 6014, who had an estimated creatinine clearance of 39 mL/min prior to randomization.

Six subjects had a serum urate level of <8.0 mg/dL at the Screening Visit without concomitant uric acid-lowering therapy (3 febuxostat 120 mg QD, 1 febuxostat 240 mg QD, and 2 allopurinol 300/100 mg QD).

Five subjects had concomitant therapy with aspirin-containing medication or other salicylates (1 placebo, 2 febuxostat 80 mg QD, 1 febuxostat 120 mg QD, and 1 febuxostat 240 mg QD). All the salicylate use was on an as needed basis.

Two febuxostat 80 mg QD subjects had concomitant urate-lowering therapy.

Subject 4485 discontinued the medication (Hyzaar) during the study; Subject 4855 prematurely discontinued from the study due to the exclusionary medication (Cozaar).

One febuxostat 80 mg QD subject (4640) had a Day -2 serum urate level <8.0 mg/dL, as determined by the central laboratory. The urate level was repeated prior to randomization and was >8.0 mg/dL. Five additional febuxostat 80 mg QD subjects (4201, 4430, 4626, 4695, and 4976) were excluded from the efficacy analysis due to serum urate levels <8.0 mg/dL based on the analysis window (ie, the last visit prior to Day 1).

One placebo subject (4720) was enrolled with a significant medical condition of chronic atrial fibrillation that was controlled with medications .

Two febuxostat 120 mg QD subject (4074 and 4274) was entered in the study with active rheumatoid arthritis requiring treatment with Tylenol arthritis and rofecoxib, respectively.

One allopurinol 300 mg QD subject (5004) had a history of colon cancer diagnosed in 1999. A colon resection had been done, no chemotherapy was given, and the subject had been cancer free since 1999.

Table 27 : Listing of protocol deviations

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Protocol Deviation	Placebo	Febuxostat 80 mg QD	Febuxostat 120 mg QD	Febuxostat 240 mg QD	Allopurinol 300/100 mg QD
<b>Inclusion Criteria</b>					
Normal renal function	6040 <sup>a</sup>	6009 <sup>a</sup> , 6021 <sup>a</sup> , 6039 <sup>a</sup>	6029 <sup>a</sup>		4455, 6028 <sup>a</sup> , 6038 <sup>a</sup>
Serum creatinine level ≤2.0 mg/dL on Day -2		6014 <sup>a</sup> , 6021 <sup>a</sup>			6028 <sup>a</sup>
Serum urate level ≥8.0 mg/dL on Day -2		4201, 4430, 4626, 4640 <sup>a</sup> , 4695, 4976			
<b>Exclusion Criteria</b>					
Thiazide diuretic therapy	4422, 4508, 4568	4459, 4485, 4914 <sup>a</sup>	4954, 4970, 6037	4681, 4948, 4975 <sup>a</sup> , 6019	4058 <sup>a</sup> , 4141
History of renal calculi	4044, 4175, 4183	4283, 4326, 4673	4218 <sup>a</sup> , 4251, 4580	4278, 4630	4095 <sup>a</sup> , 4119, 4125, 4301, 4669, 4890
Concomitant therapy with any systemic or topical medications containing aspirin or other salicylates at the Screening Visit	4921	4240 <sup>a</sup> , 4439	4749	4876	
Alcohol intake ≥14 drinks/week		4450, 4467 <sup>a</sup> , 4573, 4593 <sup>a</sup> , 4920 <sup>a</sup>	4258 <sup>a</sup> , 4543 <sup>a</sup> , 4610, 4870 <sup>a</sup>	4229 <sup>a</sup> , 4390, 5011 <sup>a</sup>	4088, 4729, 4942
Concomitant urate- lowering therapy		4485 <sup>a</sup> , 4855			
Active liver disease or hepatic dysfunction	4217 <sup>a</sup> , 4257 <sup>a</sup>	4191 <sup>a</sup> , 4226 <sup>a</sup>	4162, 4281 <sup>a</sup> , 4312 <sup>a</sup> , 4567 <sup>a</sup> , 4644 <sup>a</sup>		4498 <sup>a</sup> , 4637 <sup>a</sup> , 4654 <sup>a</sup>
Significant medical condition	4720 <sup>a</sup>				
Serum urate level <8.0 mg/dL and not taking uric acid-lowering therapy			4072 <sup>a</sup> , 4138 <sup>a</sup> , 4882 <sup>a</sup>	4966 <sup>a</sup>	4284 <sup>a</sup> , 4713 <sup>a</sup>
Active rheumatoid arthritis requiring treatment (other than prednisone)			4074 4274		
History of cancer					5004 <sup>a</sup>

<sup>a</sup> Protocol departure granted by sponsor.  
 Cross-reference: Appendices 16.2-2.1 and 16.2-3.1.

**Table 28: concomitant med deviation**

	Treatment Group n (%)				
	Placebo (N=134)	Febuxostat 80 mg QD (N=267)	Febuxostat 120 mg QD (N=269)	Febuxostat 240 mg QD (N=134)	Allopurinol 300/100 mg QD (N=268)
<b>Prohibited Medications</b>					
Allopurinol	0	2 (1%)	0	0	0
Chronic (>100 consecutive days) NSAIDs use	11 (8%)	17 (6%)	23 (9%)	9 (7%)	21 (8%)
Losartan potassium	1 (1%)	3 (1%)	1 (<1%)	0	3 (1%)
Methotrexate	1 (1%)	0	0	0	0
Salicylate-containing medications (other than low-dose aspirin)	1 (1%)	4 (1%)	10 (4%)	1 (1%)	6 (2%)
Thiazide diuretics	3 (2%)	8 (3%)	5 (2%)	4 (3%)	4 (1%)
Trimethoprim-sulfamethoxazole	1 (1%)	0	3 (1%)	1 (1%)	0
<b>Allowed Medications Above Low, Stable Doses</b>					
Ascorbic acid (>500 mg/day)	2 (1%)	4 (1%)	6 (2%)	2 (1%)	3 (1%)
Aspirin (>325 mg/day)	4 (3%)	2 (1%)	3 (1%)	3 (2%)	6 (2%)
Nicotinic acid (>500 mg/day)	0	2 (1%)	1 (<1%)	2 (1%)	1 (<1%)
Prednisone (>10 mg/day)	21 (16%)	42 (16%)	36 (13%)	26 (19%)	35 (13%)
<b>Allowed Medications Not on an as Needed Basis</b>					
Acetaminophen	0	3 (1%)	5 (2%)	2 (1%)	5 (2%)

Cross-reference: Appendices 16.2-7.4.1 and 16.2-7.4.2

#### 4.2 Demographics

**Table 29: number of subjects in each data set analyzed**

	Placebo	Febuxostat 80 mg QD	Febuxostat 120 mg QD	Febuxostat 240 mg QD	Allopurinol 300/100 mg QD
All Randomized Subjects	134	267	269	134	268
ITT Subjects <sup>a</sup>	134	262	269	134	268
PK/PD Subjects	44	82	71	35	78

a Defined as randomized subjects who took at least 1 dose of study drug and had serum urate levels  $\geq 8.0$  mg/dL at the last visit prior to Day 1.

Cross-reference: Statistical Table 14.1.2.1

*Reviewers comments: except for 5 subjects in the feb80 group, all randomized subjects were included in the ITT population.*

**Table 30 : Baseline demographics**

Variable	Placebo (N=134) n (%)	Febuxostat 80 mg QD (N=267) n (%)	Febuxostat 120 mg QD (N=269) n (%)	Febuxostat 240 mg QD (N=134) n (%)	Allopurinol 300/100 mg QD (N=268) n (%)	All Subjects (N=1072) n (%)
<b>Gender</b>						
Female	11 (8%)	16 (6%)	13 (5%)	8 (6%)	19 (7%)	67 (6%)
Male	123 (92%)	251 (94%)	256 (95%)	126 (94%)	249 (93%)	1005 (94%)
<b>Race</b>						
Caucasian	108 (81%)	200 (75%)	214 (80%)	107 (80%)	206 (77%)	835 (78%)
Black	9 (7%)	38 (14%)	27 (10%)	13 (10%)	33 (12%)	120 (11%)
Hispanic	10 (7%)	13 (5%)	16 (6%)	8 (6%)	17 (6%)	64 (6%)
Asian	3 (2%)	8 (3%)	8 (3%)	1 (1%)	6 (2%)	26 (2%)
Other	4 (3%)	8 (3%)	4 (1%)	5 (4%)	6 (2%)	27 (3%)
<b>Age (years)<sup>a</sup></b>						
<45	36 (27%)	82 (31%)	79 (29%)	33 (25%)	82 (31%)	312 (29%)
45-<65	79 (59%)	146 (55%)	154 (57%)	71 (53%)	147 (55%)	597 (56%)
≥65	19 (14%)	39 (15%)	36 (13%)	30 (22%)	39 (15%)	163 (15%)
Mean (SD)	51.5 (12.18)	50.6 (12.24)	51.2 (11.57)	54.3 (12.83)	51.8 (12.25)	51.6 (12.17)
Range	26-82	22-84	26-81	30-82	24-84	22-84
<b>Weight (pounds)<sup>a, #</sup></b>						
Mean (SD)	215.2 (43.05)	227.6 (43.77)	230.3 (48.70)	227.2 (49.04)	224.1 (43.01)	225.8 (45.61)
Range	123-360	150-396	136-468	139-425	148-382	123-468
<b>Height (inches)<sup>a</sup></b>						
N	134	267	268	134	267	1070
Mean (SD)	69.1 (3.93)	69.9 (3.24)	69.8 (3.22)	69.7 (3.38)	69.5 (3.57)	69.7 (3.43)
Range	47-75	60-78	61-80	61-83	59-78	47-83
<b>BMI (kg/m<sup>2</sup>)<sup>a, #</sup></b>						
N	134	267	268	134	267	1070
<18.5	0	0	0	0	0	0
18.5-<25	16 (12%)	10 (4%)	11 (4%)	9 (7%)	15 (6%)	61 (6%)
25-<30	48 (36%)	85 (32%)	81 (30%)	42 (31%)	91 (34%)	347 (32%)
≥30	70 (52%)	172 (64%)	176 (65%)	83 (62%)	161 (60%)	662 (62%)
Missing	0	0	1 (<1%)	0	1 (<1%)	2 (<1%)
Mean (SD)	31.8 (6.32)	32.7 (5.75)	33.2 (6.55)	32.8 (6.55)	32.6 (5.81)	32.7 (6.15)
Range	22-53	20-55	21-63	21-65	20-50	20-65
<b>Menopausal History (females)</b>						
N	11	16	13	8	19	67
Premenopausal	0	3 (19%)	3 (23%)	0	1 (5%)	7 (10%)
Perimenopausal	0	1 (6%)	0	0	0	1 (1%)
Postmenopausal	9 (82%)	11 (69%)	10 (77%)	7 (88%)	17 (89%)	54 (81%)
Missing	2 (18%)	1 (6%)	0	1 (13%)	1 (5%)	5 (7%)
<b>Tobacco Use</b>						
Non-/Ex-Tobacco User	102 (76%)	209 (78%)	213 (79%)	110 (82%)	222 (83%)	856 (80%)
Tobacco User	32 (24%)	58 (22%)	56 (21%)	24 (18%)	46 (17%)	216 (20%)
<b>Alcohol Use</b>						
Non-/Ex-Drinker	47 (35%)	87 (33%)	97 (36%)	55 (41%)	77 (29%)	363 (34%)
Drinker	87 (65%)	180 (67%)	172 (64%)	79 (59%)	191 (71%)	709 (66%)

SD = standard deviation

# Statistically significant difference among treatment groups (p≤0.05) using ANOVA.

a At baseline.

Cross-reference: Statistical Table 14.1.3.1 and Appendices 16.2-4.1, 16.2-4.3, and 16.2-4.5

*Reviewers comments: the groups appear to be reasonably well balanced in terms of demographic factors.*

**Table 31 : Medical conditions at baseline**

Medical Condition	Placebo (N=134) n (%)	Febuxostat 80 mg QD (N=267) n (%)	Febuxostat 120 mg QD (N=269) n (%)	Febuxostat 240 mg QD (N=134) n (%)	Allopurinol 300/100 mg QD (N=268) n (%)	All Subjects (N=1072) n (%)
Congestive Heart Failure	5 (4%)	7 (3%)	7 (3%)	6 (4%)	5 (2%)	30 (3%)
Cardiovascular Disease	18 (13%)	38 (14%)	37 (14%)	24 (18%)	27 (10%)	144 (13%)
Diabetes	9 (7%)	19 (7%)	29 (11%)	12 (9%)	21 (8%)	90 (8%)
Hypercholesterolemia	8 (6%)	12 (4%)	17 (6%)	8 (6%)	16 (6%)	61 (6%)
Hyperlipidemia	44 (33%)	90 (34%)	90 (33%)	49 (37%)	76 (28%)	349 (33%)
Hypertension	61 (46%)	124 (46%)	124 (46%)	70 (52%)	123 (46%)	502 (47%)
Obesity <sup>a</sup>	70 (52%)	172 (64%)	176 (65%)	83 (62%)	161 (60%)	662 (62%)
Use of Low-dose Aspirin <sup>b,c</sup>	30 (22%)	46 (17%)	39 (14%)	34 (25%)	34 (13%)	183 (17%)
Metabolic Syndrome <sup>c</sup>	11 (8%)	27 (10%)	20 (7%)	11 (8%)	20 (7%)	89 (8%)
Serum Creatinine (mg/dL) <sup>d</sup>						
≤1.5	129 (96%)	258 (97%)	258 (96%)	129 (96%)	258 (96%)	1032 (96%)
>1.5	5 (4%)	9 (3%)	11 (4%)	5 (4%)	10 (4%)	40 (4%)
Measured Creatinine Clearance (mL/min/1.73 m <sup>2</sup> ) <sup>e</sup>						
<50	12 (9%)	20 (7%)	25 (9%)	8 (6%)	24 (9%)	89 (8%)
≥50	119 (89%)	236 (88%)	233 (87%)	125 (93%)	235 (88%)	948 (88%)
Missing	3 (2%)	11 (4%)	11 (4%)	1 (1%)	9 (3%)	35 (3%)

# Statistically significant difference among treatment groups (p≤0.05) using Chi-square test.

a Body mass index ≥30 kg/m<sup>2</sup>.

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

c Defined as subjects who met all of the following criteria at baseline: triglycerides ≥150 mg/dL, systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥85 mm Hg, and fasting glucose ≥110 mg/dL.

d At baseline.

e 24-hour measured creatinine clearance at baseline.

Cross-reference: Statistical Table 14.1.3.1 and Appendices 16.2-4.1, 16.2-4.2, 16.2-7.4.1, 16.2-8.4.1, 16.2-8.4.2, 16.2-8.4.4, 16.2-8.5.1 and 16.2-8.9.1

*Reviewers comments: the groups are balanced in terms of the above. The slight differences in terms of ASA use could potentially favor febuxostat over placebo since low dose ASA use may lead to increases in serum uric. However ASA use is similar to that in the allopurinol group. Measures of creatinine appear to be similar between groups.*

Clinical Review  
{Schiffenbauer, Joel}  
{NDA 21-856}  
{Uloric/febuxostat}

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**Table 32 : Baseline gout characteristics**

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Variable	Placebo (N=134) n (%)	Febuxostat 80 mg QD (N=267) n (%)	Febuxostat 120 mg QD (N=269) n (%)	Febuxostat 240 mg QD (N=134) n (%)	Allopurinol 300/100 mg QD (N=268) n (%)	All Subjects (N=1072) n (%)
<b>Years with Gout</b>						
Mean (SD)	9.9 (8.13)	10.9 (9.29)	11.8 (9.07)	11.0 (8.66)	10.5 (9.03)	10.9 (8.96)
Range	<1-45	<1-43	<1-43	<1-42	<1-41	<1-45
<b>Years Since Last Gout Flare</b>						
>10	1 (1%)	3 (1%)	2 (1%)	0	1 (<1%)	7 (1%)
6-10	0	0	4 (1%)	2 (1%)	4 (1%)	10 (1%)
1-5	13 (10%)	29 (11%)	24 (9%)	16 (12%)	21 (8%)	103 (10%)
<1	120 (90%)	235 (88%)	239 (89%)	116 (87%)	242 (90%)	952 (89%)
<b>Previous Use of Urate-Lowering Therapy</b>						
Prior use	32 (24%)	89 (33%)	97 (36%)	49 (37%)	90 (34%)	357 (33%)
No prior use	102 (76%)	178 (67%)	172 (64%)	85 (63%)	178 (66%)	715 (67%)
<b>History or Presence of a Tophus</b>						
Yes	44 (33%)	64 (24%)	79 (29%)	36 (27%)	76 (28%)	299 (28%)
No	90 (67%)	203 (76%)	190 (71%)	98 (73%)	192 (72%)	773 (72%)
<b>Years Since First Tophus Onset<sup>a</sup></b>						
N	44	63	79	35	76	297
Mean (SD)	6.1 (5.28)	5.9 (6.37)	5.3 (6.07)	4.7 (4.48)	6.3 (7.13)	5.7 (6.14)
Range	<1-20	<1-26	<1-34	<1-15	<1-35	<1-35
<b>Presence of a 1° Palpable Tophus</b>						
Yes	29 (22%)	48 (18%)	53 (20%)	25 (19%)	64 (24%)	219 (20%)
No, but other tophi present	1 (1%)	0	3 (1%)	1 (1%)	1 (<1%)	6 (1%)
No, and no other tophi present	104 (78%)	219 (82%)	213 (79%)	108 (81%)	203 (76%)	847 (79%)
<b>Total No. of Palpable Tophi Present<sup>b</sup></b>						
N	30	48	56	26	65	225
Mean (SD)	2.8 (4.25)	3.4 (5.95)	3.9 (6.07)	2.1 (1.16)	2.6 (4.70)	3.1 (5.06)
Range	1-22	1-39	1-33	1-4	1-37	1-39
<b>Site of 1° Palpable Tophus<sup>c</sup></b>						
N	29	48	53	25	64	219
Wrist/hand	6 (21%)	9 (19%)	5 (9%)	2 (8%)	6 (9%)	28 (13%)
Ankle/foot/toe/instep	7 (24%)	16 (33%)	19 (36%)	14 (56%)	31 (48%)	87 (40%)
Elbow	14 (48%)	18 (38%)	16 (30%)	8 (32%)	20 (31%)	76 (35%)
Knee	1 (3%)	3 (6%)	3 (6%)	0	2 (3%)	9 (4%)
Other	1 (3%)	2 (4%)	10 (19%)	1 (4%)	5 (8%)	19 (9%)
<b>Size of 1° Palpable Tophus (mm<sup>2</sup>)<sup>c</sup></b>						
N	29	48	53	25	64	219
Mean (SD)	1547.8 (1739.44)	2227.1 (3506.87)	1648.5 (2836.08)	1376.7 (1657.13)	1147.0 (1893.35)	1584.4 (2539.72)
Range	16-7650	8-18750	4-14375	25-5986	6-9898	4-18750

SD = standard deviation

a Included only subjects with a history or presence of a tophus at baseline.

b Included only subjects who had a palpable tophus identified at baseline.

c Included only subjects who had a primary palpable tophus identified at baseline.

Cross-reference: Statistical Table 14.1.4.1 and Appendices 16.2-4.2, 16.2-4.4.1, 16.2-4.4.2, 16.2-6.3.1, 16.2-6.3.2, and 16.2-7.4.2

*Reviewers comments: years with gout and previous uric acid lowering therapy are similar between the treatment groups. The clinical difference in size of tophus etc is not known.*

**Table 33 : Baseline serum urate levels**

Baseline Serum Urate (mg/dL)	Placebo (N=134) n (%)	Febuxostat 80 mg QD (N=262) n (%)	Febuxostat 120 mg QD (N=269) n (%)	Febuxostat 240 mg QD (N=134) n (%)	Allopurinol 300/100 mg QD (N=268) n (%)	All ITT Subjects (N=1067) n (%)
<9.0	34 (25%)	61 (23%)	75 (28%)	36 (27%)	79 (29%)	285 (27%)
9.0 to <10.0	51 (38%)	90 (34%)	80 (30%)	48 (36%)	97 (36%)	366 (34%)
10.0 to <11.0	26 (19%)	58 (22%)	66 (25%)	25 (19%)	46 (17%)	221 (21%)
11.0 to <12.0	13 (10%)	34 (13%)	31 (12%)	18 (13%)	29 (11%)	125 (12%)
≥12.0	10 (7%)	19 (7%)	17 (6%)	7 (5%)	17 (6%)	70 (7%)
Mean (SD)	9.80 (1.367)	9.96 (1.329)	9.88 (1.225)	9.81 (1.191)	9.78 (1.216)	9.85 (1.263)
Range	6.7-16.1	7.5-15.0	7.5-14.1	7.5-13.1	7.4-14.4	6.7-16.1

SD = standard deviation

Note: Baseline was defined as the average of the serum urate measurements within the baseline window (Day -10 to 1). If a subject had more than 3 measurements within the baseline window, the last 3 measurements were used.

Cross-reference: Statistical Table 14.1.5 and Appendix 16.2-6.1.1

*Reviewers comments: baseline serum urate levels are similar in all groups.*

**Table 34 : study compliance**

Compliance	Placebo (N=134) n (%)	Febuxostat 80 mg QD (N=262) n (%)	Febuxostat 120 mg QD (N=269) n (%)	Febuxostat 240 mg QD (N=134) n (%)	Allopurinol 300/100 mg QD (N=268) n (%)
<80%	1 (1%)	10 (4%)	5 (2%)	0	8 (3%)
80 to <90%	10 (7%)	21 (8%)	26 (10%)	6 (4%)	20 (7%)
≥90%	123 (92%)	231 (88%)	238 (88%)	128 (96%)	240 (90%)
Mean (SD)	97.3 (4.28)	95.7 (8.56)	96.7 (5.36)	97.8 (3.67)	96.0 (6.61)
Range	76-100	17-100	70-100	80-100	52-100

Cross-reference: Statistical Table 14.1.8.2 and Appendices 16.2-5.2.1 to 12.6-5.2.3

*Reviewers comments: Compliance is comparable between groups.*

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4.3 Efficacy

The primary outcome measure was a responder analysis of individuals with the last 3 serum urate levels less than 6 mg/dl. Because the primary purpose behind a urate lowering drug is to maintain serum urate less than 6 and the belief that a sustained lowering of uric acid leads to a negative uric acid balance and therefore in the long run leads to reduced attacks of gout, uric acid stones, and tophi, the serum urate level over 3 visits was chosen as the primary outcome. The results of this analysis are presented in the next table

**Table 35 : Proportion of Subjects Whose Last 3 Serum Urate Levels were <6 mg/dl- ITT subjects**

Last 3 Serum Urate Levels	Placebo		Febuxostat 80 mg QD		Febuxostat 120 mg QD		Febuxostat 240 mg QD		Allopurinol 300/100 mg QD	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
<6.0 mg/dL										
Yes	0/134	(0%)	126/262 (48%) <sup>p,m,h</sup>		175/269 (65%) <sup>p</sup>		92/134 (69%) <sup>p,a</sup>		60/268 (22%) <sup>p</sup>	
No	134/134 (100%)		136/262 (52%)		94/269 (35%)		42/134 (31%)		208/268 (78%)	
			<b>Difference in Proportions</b>		<b>97.5% CI<sup>†</sup></b>		<b>P-value<sup>‡</sup></b>			
Febuxostat 80 mg vs. Allopurinol 300/100 mg			26%		(16.7% 34.7%)		<0.001 <sup>#</sup>			
Febuxostat 120 mg vs. Allopurinol 300/100 mg			43%		(34.0% 51.3%)		<0.001 <sup>#</sup>			

† 97.5% CI = 97.5% confidence interval for the difference in proportions based on the normal approximation for the binomial distribution

‡ P-values from a CMH test stratified by baseline renal function (serum creatinine ≤1.5 mg/dL vs. >1.5 mg/dL)

# Statistically significant difference versus allopurinol 300/100 mg QD at the 0.05 level using Hochberg's procedure for multiple comparisons

p Statistically significant difference versus placebo (p≤0.05) (Hochberg's procedure for multiple comparisons was used for comparisons of the febuxostat treatment groups versus placebo)

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

m Statistically significant difference versus febuxostat 120 mg QD (p≤0.05).

h Statistically significant difference versus febuxostat 240 mg QD (p≤0.05).

Cross-reference: Statistical Table 14.2.1.1 and Appendix 16.2-6.1.1

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Clinical Review  
 {Schiffenbauer, Joel}  
 {NDA 21-856}  
 {Uloric/febuxostat}

Proportion of Subjects with Last Three Serum Urate Levels < 6.0 mg/dL - ITT Subjects  
 Subjects who Completed the Study

	Placebo	Febuxostat 80 mg QD	Febuxostat 120 mg QD	Febuxostat 240 mg QD	Allopurinol 300/100 mg 2D
Last 3 Serum Urate < 6.0 mg/dL					
Yes	0.04 ( 0/101)	58.04 ( 98/170)	74.00 (148/200)	83.75 ( 72/ 86)	27.04 ( 57/211)
No	100.00 (101/101)	42.04 ( 72/170)	26.00 ( 52/200)	16.25 ( 14/ 86)	73.04 (154/211)
		Difference in Proportions	97.5% CI (a)	P-value (b)	
Primary Comparisons					
Febux 80 mg vs Allo 300/100 mg		58.0%	( 26.0%, 43.0%)	<0.001#	
Febux 120 mg vs Allo 300/100 mg		47.0%	( 37.3%, 56.7%)	<0.001#	
Additional Comparisons					
Febux 80 mg vs Placebo				<0.001#	
Febux 120 mg vs Placebo				<0.001#	
Febux 240 mg vs Placebo				<0.001#	
Febux 240 mg vs Allo 300/100 mg				<0.001***	
Allo 300/100 mg vs Placebo				<0.001***	
Febux 80 mg vs Febux 120 mg				0.001***	
Febux 80 mg vs Febux 240 mg				<0.001***	
Febux 120 mg vs Febux 240 mg				0.064	

(a) 97.5% confidence interval for the difference in proportions based on the normal approximation for the binomial distribution.  
 (b) P-values are from a Cochran-Mantel-Haenszel test stratified by baseline renal function (serum creatinine < 1.5 or > 1.5 mg/dL).  
 # Indicates statistical significance at the 0.05 level versus Allopurinol 300/100 mg QD based on Hochberg's procedure for multiple comparisons.  
 \*\* Indicates statistical significance at the 0.05 level versus placebo based on Hochberg's procedure for multiple comparisons.  
 \*, \*\*, \*\*\* indicates statistical significance at the 0.05, 0.01, or 0.001 level, respectively.

*Reviewers comments: this analysis clearly demonstrates the efficacy of febuxostat in lowering serum urate levels. Based on this analysis, all doses of febuxostat appear superior to allopurinol in lowering serum urate levels to less than 6 mg/dL. There is marginal increased benefit at the 240 mg dose (although the sponsor does not propose this dose for labeling). However, the sponsor originally predicted (based on the literature and their own data) that the allopurinol response rate would approach 60%. This is not the case, and the concern is either that the sponsors original prediction was wrong, or that there is something wrong with the allopurinol used in the trials (this includes trial 010 which gave similar results). The pharmacologists are pursuing this issue by obtaining samples of the allopurinol used in the trials for further analysis.*

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Additional analyses are provided below.

**Table 36 : Proportion of Subjects Whose Last 3 Serum Urate Levels were <6.0 mg/dL by Baseline Serum Creatinine Levels - ITT Subjects**

Baseline Serum Creatinine Level	Placebo		Febuxostat 80 mg QD <sup>p,a,m,h</sup>		Febuxostat 120 mg QD <sup>b,a</sup>		Febuxostat 240 mg QD <sup>b,a</sup>		Allopurinol 300/100 mg QD <sup>p</sup>	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
≤1.5 mg/dL	0/129	(0%)	122/253	(48%)	170/258	(66%)	89/129	(69%)	60/258	(23%)
> 1.5 mg/dL	0/5	(0%)	4/9	(44%)	5/11	(45%)	3/5	(60%)	0/10	(0%)

Subjects with baseline serum creatinine ≤1.5 mg/dL received allopurinol 300 mg QD (n=258) and subjects with baseline serum creatinine >1.5 mg/dL received allopurinol 100 mg QD (n=10).

Comparisons between treatment groups were made with a CMH test stratified by baseline serum creatinine level.

p Statistically significant difference versus placebo (p≤0.05)

a Statistically significant difference versus allopurinol 300/100 mg QD (p≤0.05)

m Statistically significant difference versus febuxostat 120 mg QD (p≤0.05)

h Statistically significant difference versus febuxostat 240 mg QD (p≤0.05)

Cross-reference: Statistical Table 14.2.1.3 and Appendix 16.2-6.1.1

*Reviewers comments: There are very few subjects with serum creatinine greater than 1.5. Firm conclusions about the efficacy of febuxostat in this population can not be reached based on this study.*

Response rates also were compared using CMH methodology adjusting for gender, age, race, overall compliance, baseline measured creatinine clearance, baseline serum urate level, baseline palpable tophus presence, previous use of urate-lowering therapy, history of cardiovascular risk factors, alcohol use, baseline BMI, use of low-dose aspirin, tobacco use, and presence of metabolic syndrome (analysis not shown)

After adjusting for each factor, statistically significant pairwise differences were observed between each of the active treatment groups and the placebo group, with higher response rates observed in the active treatment groups (p<0.001). Additionally, statistically significant pairwise differences were noted between each of the febuxostat groups and the allopurinol 300/100 mg QD group, with higher response rates observed in the febuxostat treatment groups (p<0.001). Furthermore, the difference between the febuxostat 80 mg QD and each of the other febuxostat treatment groups was statistically significant (p<0.001) after adjusting for each factor with response rates increasing with dose

Clinical Review  
 {Schiffenbauer, Joel}  
 {NDA 21-856}  
 {Uloric/febuxostat}

**Table 37 : Proportion of Subjects Whose Last 3 Serum Urate Levels were  
 <6.0 mg/dL by Baseline Serum Urate - ITT Subjects**

Baseline Serum Urate Level	Placebo	Febuxostat 80 mg QD <sup>n,a,m,h</sup>	Febuxostat 120 mg QD <sup>n,a</sup>	Febuxostat 240 mg QD <sup>n,a</sup>	Allopurinol 300/100 mg QD <sup>p</sup>
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
<9.0 mg/dL	0/34 (0%)	40/61 (66%)	57/75 (76%)	24/36 (67%)	29/79 (37%)
9.0 to <10.0 mg/dL	0/51 (0%)	46/90 (51%)	59/80 (74%)	35/48 (73%)	22/97 (23%)
≥10.0 mg/dL	0/49 (0%)	40/111 (36%)	59/114 (52%)	33/50 (66%)	9/92 (10%)

Comparisons between treatment groups were made with a CMH test stratified by baseline serum urate level.

p Statistically significant difference versus placebo (p≤0.05)

a Statistically significant difference versus allopurinol 300/100 mg QD (p≤0.05)

m Statistically significant difference versus febuxostat 120 mg QD (p≤0.05)

h Statistically significant difference versus febuxostat 240 mg QD (p≤0.05)

Cross-reference: Statistical Table 14.2.1.3 and Appendix 16.2-6.1.1

*Reviewers comments: Febuxostat appears to be superior to allopurinol at any baseline serum urate level.*

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Secondary outcomes:

The following sensitivity analysis was requested from the sponsor.

**Table 38 : serum urate levels less than 6 after week 4**

Proportion of subjects with All Serum Urate Levels < 6.0 mg/dL after Week 4 - ITT Subjects

	Placebo	Febuxostat 80 mg QD	Febuxostat 120 mg QD	Febuxostat 240 mg QD	Allopurinol 300/100 mg QD
All Serum Urate < 6.0 mg/dL					
Yes	3.0% ( 9/120)	46.3% (127/274)	50.9% (151/297)	73.0% ( 85/116)	39.1% ( 44/243)
No	100.0% (120/120)	53.7% (124/231)	49.1% ( 97/249)	26.1% ( 10/115)	61.0% (199/243)
		Difference in Proportions	97.5% CI (a)	P-values (b)	
<b>Primary Comparisons</b>					
Febux 80 mg vs Allo 300/100 mg		28.3%	( 19.0%, 37.4%)	<0.001#	
Febux 120 mg vs Allo 300/100 mg		42.9%	( 33.9%, 51.7%)	<0.001#	
<b>Additional Comparisons</b>					
Febux 80 mg vs Placebo				<0.001##	
Febux 120 mg vs Placebo				<0.001##	
Febux 240 mg vs Placebo				<0.001##	
Febux 240 mg vs Allo 300/100 mg				<0.001***	
Allo 300/100 mg vs Placebo				<0.001***	
Febux 80 mg vs Febux 120 mg				<0.001***	
Febux 80 mg vs Febux 240 mg				<0.001***	
Febux 120 mg vs Febux 240 mg				<0.01*	

Successor subjects are defined as serum urate < 6.0 mg/dL for every visit on week 5 of later.  
 The denominator for each treatment group is the number of subjects with at least one visit on week 5 or later.  
 (a) 97.5% confidence interval for the difference in proportions based on the normal approximation for the binomial distribution.  
 (b) P-values are from a Cochran-Mantel-Haenszel test stratified by baseline renal function (serum creatinine < 1.5 vs > 1.5 mg/dL).  
 # Indicates statistical significance at the 0.05 level versus placebo based on Hochberg's procedure for multiple comparisons.  
 ## Indicates statistical significance at the 0.05 level versus placebo based on Hochberg's procedure for multiple comparisons.  
 \*, \*\*, \*\*\* indicates statistical significance at the 0.05, 0.01, or 0.001 level, respectively.

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**Table 39: completers**

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Clinical Review  
 {Schiffenbauer, Joel}  
 {NDA 21-856}  
 {Uloric/febuxostat}

Proportion of Subjects with All Serum Urate Levels < 6.0 mg/dL after Week 4 - ITT Subjects  
 Subjects who Completed the Study

	Placebo	Febuxostat 80 mg QD	Febuxostat 120 mg QD	Febuxostat 240 mg QD	Allopurinol 300/100 mg QD
All Serum Urate < 6.0 mg/dL					
Yes	0.01 ( 0/101)	48.7% ( 78/160)	62.0% (124/200)	78.3% ( 61/ 86)	17.9% ( 37/211)
No	100.0% (101/101)	51.3% ( 82/160)	38.0% ( 76/200)	21.7% ( 19/ 86)	82.1% (174/211)
		Difference in Proportions	97.5% CI (a)	P-values (b)	
Primary Comparisons					
Febux 80 mg vs Allo 300/100 mg		48.2%	( 18.8%, 79.6%)	<0.001#	
Febux 120 mg vs Allo 300/100 mg		44.5%	( 24.8%, 64.1%)	<0.001#	
Additional Comparisons					
Febux 80 mg vs Placebo				<0.001##	
Febux 120 mg vs Placebo				<0.001##	
Febux 240 mg vs Placebo				<0.001##	
Febux 240 mg vs Allo 300/100 mg				<0.001***	
Allo 300/100 mg vs Placebo				<0.001***	
Febux 80 mg vs Febux 120 mg				0.004**	
Febux 80 mg vs Febux 240 mg				<0.001***	
Febux 120 mg vs Febux 240 mg				0.677	

Success subjects are defined as serum urate < 6.0 mg/dL for every visit on week 4 or later.  
 The denominator for each treatment group is the number of subjects who completed the study.  
 (a) 97.5% confidence interval for the difference in proportions based on the normal approximation for the binomial distribution.  
 (b) P-values are from a Cochran-Mantel-Haenszel test stratified by baseline renal function (serum creatinine < 1.5 vs ≥ 1.5 mg/dL).  
 # Indicates statistical significance at the 0.05 level versus Allopurinol 300/100 mg QD based on Hochberg's procedure for multiple comparisons.  
 ## Indicates statistical significance at the 0.05 level versus placebo based on Hochberg's procedure for multiple comparisons.  
 \*, \*\*, \*\*\* indicates statistical significance at the 0.05, 0.01, or 0.001 level, respectively.

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*Reviewers comments: The key to treating hyperuricemia is to maintain the urate level below 6 for an extended period of time to allow for reduction of total body urate. This is a robust analysis which demonstrates that serum urate levels can be maintained below 6 for many months, and demonstrates the superiority of febuxostat over allopurinol.*

**Table 40 : Proportion of Subjects with Serum Urate Levels <6.0 mg/dL, <5.0 mg/dL, and <4.0 mg/dL at the Week 28 and Final Visits – ITT Subjects**

Visit	Placebo		Febuxostat 80 mg QD <sup>p,a,h</sup>		Febuxostat 120 mg QD <sup>p,a</sup>		Febuxostat 240 mg QD <sup>p,a</sup>		Allopurinol 300/100 mg QD	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
<b>&lt;6.0 mg/dL</b>										
Week 28	1/99	(1%)	122/161 (76%) <sup>m</sup>		163/188 (87%)		78/83 (94%)		85/208 (41%) <sup>p</sup>	
Final	1/127	(1%)	183/253 (72%)		209/265 (79%) <sup>h</sup>		116/126 (92%)		102/263 (39%) <sup>p</sup>	
<b>&lt;5.0 mg/dL</b>										
Week 28	0/99	(0%)	82/161 (51%) <sup>m</sup>		135/188 (72%) <sup>h</sup>		72/83 (87%)		28/208 (13%) <sup>p</sup>	
Final	0/127	(0%)	116/253 (46%) <sup>m</sup>		171/265 (65%) <sup>h</sup>		106/126 (84%)		34/263 (13%) <sup>p</sup>	
<b>&lt;4.0 mg/dL</b>										
Week 28	0/99	(0%)	34/161 (21%) <sup>m</sup>		77/188 (41%) <sup>h</sup>		65/83 (78%)		5/208 (2%)	
Final	0/127	(0%)	46/253 (18%) <sup>m</sup>		100/265 (38%) <sup>h</sup>		95/126 (75%)		6/263 (2%)	

Comparisons between treatment groups made with a CMH test stratified by baseline renal function (serum creatinine  $\leq 1.5$  mg/dL vs  $> 1.5$  mg/dL).

- p Statistically significant difference versus placebo ( $p \leq 0.05$ ).
- a Statistically significant difference versus allopurinol 300/100 mg QD ( $p \leq 0.05$ ).
- m Statistically significant difference versus febuxostat 120 mg QD ( $p \leq 0.05$ ).
- h Statistically significant difference versus febuxostat 240 mg QD ( $p \leq 0.05$ ).

Footnotes displayed in the column headers indicate statistical significance at both Week 28 and the Final Visit for serum urate levels  $< 6.0$ ,  $< 5.0$ , and  $< 4.0$  mg/dL.

Cross-reference: Statistical Tables 14.2.2.1, 14.2.2.3, and 14.2.2.4 and Appendix 16.2-6.1.1

*Reviewers comments: A drug that reduces serum urate to less than 4 would be quite efficacious. Febuxostat again appears to be superior to allopurinol in this regard.*

A number of additional analyses all support the efficacy of febuxostat.

**Table 41 : Proportion of Subjects with Serum Urate Level  $< 6.0$  mg/dL at the Final Visit by Baseline Serum Urate - ITT Subjects**

Baseline Serum Urate Level	Placebo		Febuxostat 80 mg QD		Febuxostat 120 mg QD		Febuxostat 240 mg QD		Allopurinol 300/100 mg QD	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
$< 9.0$ mg/dL	1/32	(3%)	56/61 (92%) <sup>p,a</sup>		66/74 (89%) <sup>p,a</sup>		30/31 (97%) <sup>p,a</sup>		44/79 (56%) <sup>p</sup>	
9.0 to $< 10.0$ mg/dL	0/50	(0%)	65/89 (73%) <sup>p,a,h</sup>		66/78 (85%) <sup>p,a</sup>		43/46 (93%) <sup>p,a</sup>		39/95 (41%) <sup>p</sup>	
$\geq 10.0$ mg/dL	0/45	(0%)	62/103 (60%) <sup>p,a,h</sup>		77/113 (68%) <sup>p,a,h</sup>		43/49 (88%) <sup>p,a</sup>		19/89 (21%) <sup>p</sup>	

Comparisons between treatment groups were made with a CMH test stratified by baseline renal function (serum creatinine  $\leq 1.5$  mg/dL vs  $> 1.5$  mg/dL).

- p Statistically significant difference versus placebo ( $p \leq 0.05$ )
- a Statistically significant difference versus allopurinol 300/100 mg QD ( $p \leq 0.05$ )
- h Statistically significant difference versus febuxostat 240 mg QD ( $p \leq 0.05$ )

Cross-reference: Statistical Table 14.2.2.2 and Appendix 16.2-6.1.1

**Table 42 : Mean Percent Change from Baseline in Serum Urate Levels at the Week 28 and Final Visits - ITT Subjects**

Clinical Review  
 {Schiffenbauer, Joel}  
 {NDA 21-856}  
 {Uloric/febuxostat}

Visit	Placebo		Febuxostat 80 mg QD <sup>p,a,m,h</sup>		Febuxostat 120 mg QD <sup>p,a,h</sup>		Febuxostat 240 mg QD <sup>p,a</sup>		Allopurinol 300/100 mg QD <sup>p</sup>	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
<b>Actual Value (mg/dL)</b>										
Baseline Mean	134	9.80 (1.367)	262	9.96 (1.329)	269	9.88 (1.225)	134	9.81 (1.191)	268	9.78 (1.216)
Week 28	99	9.25 (1.544)	161	5.15 (1.678)	188	4.41 (1.498)	83	3.18 (1.897)	208	6.35 (1.456)
Final	127	9.45 (1.611)	253	5.41 (1.892)	265	4.76 (1.901)	126	3.32 (2.080)	263	6.45 (1.517)
<b>Percent Change from Baseline (%)</b>										
Week 28	99	-3.58 (13.846)	161	-47.58 (15.861)	188	-54.88 (14.965)	83	-67.83 (18.182)	208	-34.35 (14.210)
Final Visit	127	-2.99 (13.283)	253	-45.23 (18.157)	265	-51.89 (17.989)	126	-66.32 (20.616)	263	-33.70 (14.745)

Comparisons between treatment groups were made with a two-way ANOVA with treatment and baseline renal function (serum creatinine ≤1.5 mg/dL vs. >1.5 mg/dL) as factors.  
 Note: Baseline was defined as the average of serum urate measurements within the baseline window (Days -10 to 1).  
 If a subject had more than 3 measurements within the baseline window, the last 3 measurements were used.

- p Statistically significant difference versus placebo (p≤0.05)
- a Statistically significant difference versus allopurinol 300/100 mg QD (p≤0.05)
- m Statistically significant difference versus febuxostat 120 mg QD (p≤0.05)
- h Statistically significant difference versus febuxostat 240 mg QD (p≤0.05)

Footnotes displayed in the column headers indicate statistical significance at both Week 28 and the Final Visit.

Cross-reference: Statistical Table 14.2.2.5 and Appendix 16.2-6.1.1

Not every subject had a tophus at baseline. Therefore, these analyses are not of randomized populations and should only be considered exploratory.

**Table 43 : Median and Mean Percent Change from Baseline in Primary Tophus Size at the Week 28 and Final Visits - ITT Subjects with a Primary Palpable Tophus at Baseline**

Visit	Placebo			Febuxostat 80 mg QD			Febuxostat 120 mg QD			Febuxostat 240 mg QD			Allopurinol 300/100 mg QD		
	N	Median (25 <sup>th</sup> p., 75 <sup>th</sup> p.)	Mean	N	Median (25 <sup>th</sup> p., 75 <sup>th</sup> p.)	Mean	N	Median (25 <sup>th</sup> p., 75 <sup>th</sup> p.)	Mean	N	Median (25 <sup>th</sup> p., 75 <sup>th</sup> p.)	Mean	N	Median (25 <sup>th</sup> p., 75 <sup>th</sup> p.)	Mean
<b>Actual Value (mm<sup>3</sup>)</b>															
Baseline	29	840.0 (500.0, 2310.0)	1547.8	46	822.0 (500.0, 2601.0)	2313.7	53	575.0 (255.0, 1800.0)	1618.5	25	650.0 (340.0, 1761.0)	1376.7	64	440.0 (225.0, 1050.0)	1147.0
Week 28	21	400.0 (144.0, 1000.0)	938.2	26	760.0 (236.0, 1800.0)	1706.8	35	100.0 (0.0, 750.0)	941.8	14	150.0 (0.0, 625.0)	519.3	46	255.0 (12.0, 528.0)	500.1
Final	26	387.5 (121.0, 1000.0)	853.2	42	662.5 (150.0, 1600.0)	1414.1	50	195.0 (12.0, 924.0)	1439.9	24	280.0 (54.0, 855.0)	666.3	61	283.0 (91.0, 840.0)	722.6
<b>Percent Change from Baseline (%)</b>															
Week 28	21	-52.0 (-62.5, -21.4)	-33.8	26	-45.6 (-85.9, 3.0)	-22.0	35	-54.2 (-100.0, -16.7)	-47.3	14	-53.2 (-77.8, -22.1)	-52.7	46	-31.5 (-95.0, 3.6)	-23.1
Final	26	-40.3 (-62.5, -16.7)	-33.7	42	-33.8 (-85.4, 0.0)	-21.4	50	-42.4 (-90.3, 0.0)	-17.5	24	-47.0 (-89.0, -13.8)	-41.4	61	-22.6 (-66.7, 0.0)	-13.3

Note: Baseline was defined as the last examination prior to the first dose of study drug.  
 25<sup>th</sup> p. = 25<sup>th</sup> percentile; 75<sup>th</sup> p. = 75<sup>th</sup> percentile  
 Cross-reference: Statistical Table 14.2.2.6 and Appendices 16.2-6.3.1 and 16.2-6.3.2

*Reviewers comments: It is not clear why the change in tophus size is similar between placebo and feuxostat 80 and 120 mg but all are greater than allopurinol.*

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**Table 44 : Median and Mean Percent Change from Baseline in Primary Tophus Size by Average Post-baseline Serum Urate Level at the Week 28 and Final Visits - ITT Subjects with a Primary Palpable Tophus at Baseline**

Visit	Serum Urate <6.0 mg/dL			Serum Urate ≥6.0 mg/dL		
	N	Median (25 <sup>th</sup> p., 75 <sup>th</sup> p.)	Mean	N	Median (25 <sup>th</sup> p., 75 <sup>th</sup> p.)	Mean
<b>Actual Value (mm<sup>2</sup>)</b>						
Baseline	107	624.0 (255.0, 1140.0)	1267.0	100	750.0 (300.0, 2217.0)	1890.8
Week 28	77	144.0 (4.0, 625.0)	668.8	65	400.0 (100.0, 1020.0)	1166.5
Final	104	212.5 (5.0, 774.0)	691.4	95	484.0 (110.0, 1296.0)	1431.7
<b>Percent Change from Baseline (%)</b>						
Week 28	77	-51.4 (-96.0, -14.3)	-43.9	65	-39.0 (-72.8, 0.0)	-21.0
Final	104	-47.0 (-96.8, -7.6)	-37.5	95	-22.6 (-62.5, 0.0)	-8.7

Note: Baseline was defined as the last examination prior to the first dose of study drug.

25<sup>th</sup> p. = 25<sup>th</sup> percentile; 75<sup>th</sup> p. = 75<sup>th</sup> percentile

Cross-reference: Statistical Tables 14.2.2.8 and 14.2.2.9 and Appendices 16.2-6.1.1, 16.2-6.3.1, and 16.2-6.3.2

*Reviewers comments: It appears that the change in tophus size is greater for subjects whose serum urate is lowered to less than 6 (as would be anticipated). However, those with serum urate greater than 6 include the placebo treated population. Therefore it is not clear what conclusions can be reached from this table.*

**Table 45 : Median and Mean Percent Change from Baseline in Primary Tophus Size at the Week 28 and Final Visits - ITT Subjects with a Primary Palpable Tophus at Baseline and an Average Post-baseline Serum Urate Level <6.0 mg/dL**

Visit	Placebo			Febuxostat 80 mg QD			Febuxostat 120 mg QD			Febuxostat 240 mg QD			Allopurinol 300/100 mg QD		
	N	Median (25 <sup>th</sup> p., 75 <sup>th</sup> p.)	Mean	N	Median (25 <sup>th</sup> p., 75 <sup>th</sup> p.)	Mean	N	Median (25 <sup>th</sup> p., 75 <sup>th</sup> p.)	Mean	N	Median (25 <sup>th</sup> p., 75 <sup>th</sup> p.)	Mean	N	Median (25 <sup>th</sup> p., 75 <sup>th</sup> p.)	Mean
<b>Actual Value (mm<sup>2</sup>)</b>															
Baseline	0	-	-	23	729.0 (483.0, 2601.0)	2244.0	40	400.0 (210.0, 885.0)	849.5	22	781.0 (400.0, 2000.0)	1509.2	22	490.0 (195.0, 900.0)	762.5
Week 28	0	-	-	17	420.0 (0.0, 1462.0)	1531.5	29	49.0 (0.0, 272.0)	356.1	13	144.0 (36.0, 625.0)	514.9	18	264.5 (100.0, 750.0)	-468.8
Final	0	-	-	22	410.0 (0.0, 1462.0)	1551.6	39	100.0 (0.0, 400.0)	447.9	22	178.0 (36.0, 900.0)	664.3	21	270.0 (120.0, 750.0)	-480.1
<b>Percent Change from Baseline (%)</b>															
Week 28	0	-	-	17	-63.2 (-100.0, -30.7)	-34.2	29	-54.2 (-100.0, -16.7)	-50.9	13	-60.0 (-77.8, -28.6)	-56.8	18	-22.0 (-75.0, 5.6)	-52.4
Final	0	-	-	22	-53.1 (-100.0, 0.0)	-36.3	39	-52.7 (-100.0, -4.3)	-40.8	22	-52.2 (-82.5, -14.3)	-52.7	21	-25.0 (-66.3, 5.6)	-16.8

Note: Baseline was defined as the last examination prior to the first dose of study drug.

Note: No placebo subject had an average post-baseline serum urate level <6.0 mg/dL.

25<sup>th</sup> p. = 25<sup>th</sup> percentile; 75<sup>th</sup> p. = 75<sup>th</sup> percentile

Cross-reference: Statistical Table 14.2.2.8 and Appendices 16.2-6.1.1, 16.2-6.3.1, and 16.2-6.3.2

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**Table 46 : Median and Mean Percent Change from Baseline in Primary Tophus Size at the Week 28 and Final Visits - ITT Subjects with a Primary Palpable Tophus at Baseline and an Average Post-baseline Serum Urate Level >6.0 mg/dL**

Visit	Placebo			Febuxostat 80 mg QD			Febuxostat 120 mg QD			Febuxostat 240 mg QD			Allopurinol 300/100 mg QD		
	N	Median (25 <sup>th</sup> p., 75 <sup>th</sup> p.)	Mean	N	Median (25 <sup>th</sup> p., 75 <sup>th</sup> p.)	Mean	N	Median (25 <sup>th</sup> p., 75 <sup>th</sup> p.)	Mean	N	Median (25 <sup>th</sup> p., 75 <sup>th</sup> p.)	Mean	N	Median (25 <sup>th</sup> p., 75 <sup>th</sup> p.)	Mean
<b>Actual Value (mm<sup>3</sup>)</b>															
Baseline	27	900.0 (300.0, 2496.0)	1623.0	20	1095.0 (454.0, 1886.5)	1778.4	12	2812.0 (1087.5, 5775.0)	4454.0	1	576.0 (576.0, 576.0)	576.0	40	450.0 (225.0, 1247.5)	1397.8
Week 28	21	400.0 (144.0, 1000.0)	938.2	9	1030.0 (728.0, 2025.0)	2037.8	6	3302.0 (875.0, 7225.0)	3772.8	1	576.0 (576.0, 576.0)	576.0	28	232.5 (64.0, 492.0)	520.2
Final	25	400.0 (121.0, 1000.0)	878.3	19	900.0 (210.0, 1600.0)	1324.6	11	3364.0 (875.0, 7921.0)	4956.9	1	576.0 (576.0, 576.0)	576.0	39	288.0 (64.0, 960.0)	866.2
<b>Percent Change from Baseline (%)</b>															
Week 28	21	-52.0 (-62.5, -21.4)	-35.8	9	-34.4 (-55.0, 12.1)	1.1	6	-49.7 (-58.8, -30.4)	-30.2	1	0.0 (0.0, 0.0)	0.0	28	-37.0 (-59.5, 5.7)	-17.2
Final	25	-52.0 (-62.5, -21.4)	-35.1	19	0.0 (-55.0, 12.1)	-4.7	11	-6.6 (-54.0, 116.0)	65.0	1	0.0 (0.0, 0.0)	0.0	39	-13.3 (-67.0, 0.0)	-14.8

Note: Baseline was defined as the last examination prior to the first dose of study drug.  
 25<sup>th</sup> p. = 25<sup>th</sup> percentile; 75<sup>th</sup> p. = 75<sup>th</sup> percentile  
 Cross-reference: Statistical Table 14.2.2.9 and Appendices 16.2-6.1.1, 16.2-6.3.1, and 16.2-6.3.2

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### Proportion of Subjects Requiring Treatment for a Gout Flare

An important unresolved question is whether chronic treatment with febuxostat (or any urate lowering agent) will reduce the number of clinical attacks of gout to a clinically and statistically significant degree. This trial was not designed to rigorously address this question although the sponsor collected data on this point. It is also not clear for how long someone should be treated in order to demonstrate this relevant change in incidence of gouty attacks. Further, it should be emphasized that in this trial (and trial 010) gouty attacks are patient reported and were not necessarily confirmed by investigator examination.

The majority of subjects in the placebo, febuxostat 80 mg QD, febuxostat 120 mg QD, febuxostat 240 mg QD, and allopurinol 300/100 mg QD treatment groups received treatment for a gout flare during the study (55%, 57%, 62%, 66%, and 51%, respectively).

During the intended 8-week prophylaxis period (Day 1 to Week 8), a statistically significantly greater proportion of subjects in each of the febuxostat 120 mg QD (36%) and 240 mg QD (46%) treatment groups required treatment for a gout flare compared to the placebo (20%), allopurinol 300/100 mg QD (23%), and febuxostat 80 mg QD (28%)

treatment groups. Results similar to the Day 1 to Week 8 period were observed during the actual prophylaxis period, which was based on a subject's actual prophylaxis dosing dates. No statistically significant differences in the proportion of subjects requiring treatment for a gout flare were observed between treatment groups during Week 8 to Week 28 after the intended 8-week prophylaxis period. During the 28-Week Double-blind Treatment Period (Day 1 to Week 28), a statistically significantly greater proportion of subjects in each of the febuxostat 120 mg QD (62%) and 240 mg QD (66%) treatment groups required treatment for a gout flare compared to the allopurinol 300/100 mg QD treatment group (51%). During the 4-week intervals after the intended 8-week prophylaxis period, the proportion of subjects requiring treatment for a gout flare was initially higher in each treatment group than during the intended 8-week prophylaxis period, but the proportions were generally similar among treatment groups and gradually decreased over time. Of note, there were fewer subjects with flares requiring treatment during the last 4 weeks of the study (Week 24 to Week 28) in the febuxostat 80 mg QD, 120 mg QD, 240 mg QD, and allopurinol 300/100 mg QD groups (15%, 15%, 8%, and 14%, respectively) compared to the placebo group (20%), and the difference between the febuxostat 240 mg QD and placebo treatment groups was statistically significant.

**Table 47: Subjects Requiring Treatment for a Gout Flare by Time Interval - ITT Subjects**

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Time Interval	Placebo	Febuxostat 80 mg QD	Febuxostat 120 mg QD	Febuxostat 240 mg QD	Allopurinol 300/100 mg QD
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Screening	12/134 (9%)	21/262 (8%)	28/269 (10%)	13/134 (10%)	20/268 (7%)
Day 1 to Week 28	74/134 (55%)	149/262 (57%)	168/269 (62%) <sup>u</sup>	89/134 (66%) <sup>u</sup>	136/268 (51%)
Day 1 to Week 8	27/134 (20%)	73/262 (28%) <sup>m</sup>	97/269 (36%) <sup>p,h</sup>	61/134 (46%) <sup>p,m</sup>	61/268 (23%)
Week 8 to Week 28	62/119 (52%)	122/223 (55%)	129/240 (54%)	60/106 (57%)	110/237 (46%)
Week 8 to Week 12	34/118 (29%)	79/223 (35%)	97/240 (40%)	45/106 (42%)	63/237 (27%)
Week 12 to Week 16	23/112 (21%)	47/206 (23%)	47/227 (21%)	15/99 (15%)	51/227 (22%)
Week 16 to Week 20	23/107 (21%)	33/192 (17%)	35/218 (16%)	8/94 (9%)	39/220 (18%)
Week 20 to Week 24	17/104 (16%)	25/181 (14%)	29/209 (14%)	12/91 (13%)	28/217 (13%)
Week 24 to Week 28	21/103 (20%)	26/172 (15%)	30/206 (15%)	7/89 (8%) <sup>p</sup>	31/216 (14%)
During Prophylaxis <sup>c</sup>	29/133 (22%)	75/262 (29%) <sup>m</sup>	101/268 (38%) <sup>p,h</sup>	61/134 (46%) <sup>p,m</sup>	64/267 (24%)
After Prophylaxis <sup>c</sup>	62/133 (47%)	119/262 (45%)	128/268 (48%)	59/134 (44%)	108/267 (40%)

Comparisons between treatment groups were made with a CMH test stratified by baseline renal function (serum creatinine  $\leq 1.5$  mg/dL vs.  $> 1.5$  mg/dL).

Note: The numerator is the number of subjects requiring treatment for a gout flare in the time interval and treatment group being summarized. The denominator is the number of subjects exposed to at least 1 dose of that treatment in the time interval being summarized.

p Statistically significant difference versus placebo ( $p \leq 0.05$ )

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

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

h Statistically significant difference versus febuxostat 240 mg QD ( $p \leq 0.05$ )

& Based on each subject's actual prophylaxis period; denominator is the number of subjects with at least 1 prophylactic dose

Cross-reference: Statistical Table 14.2.2.11 and Appendix 16.2-6.2

*Reviewers comments: The trials was not designed to rigorously address the issue of the change in the rate of gouty attacks due to urate lowering therapy. This analysis did not impute missing data and is not an ITT analysis.*

*During weeks 1-8 subjects were treated with colchicine or a NSAID to prevent gout flares, which is considered the standard of care. Therefore the gout attack rate is relatively low. However, it is noted that the gout attack rate increases somewhat for subsequent weeks 8-12, and then slowly drops off until weeks 24-28. At the 20-24 week period, gouty attack rates are essentially the same in all groups (including allopurinol group, even though there is less urate lowering in the allopurinol group, see previous tables). During the 24-28 week time period, it appears that the rate of new attacks is lowest in the febuxostat 240 mg group and highest in the placebo treated group. Nevertheless, the rate of attacks is not statistically different between the placebo vs 80 or 120 mg groups. Further, the impression is that if subjects were followed for longer periods the rates in the placebo and febuxostat treatment groups would diverge even further. Reduction in the number of gouty attacks appears to occur (at least in part) because the rate of attacks increases with the initiation of urate lowering therapy (see rate for weeks 1-8).*

*This analysis suggests that febuxostat has an effect on gouty attacks but does not provide conclusive evidence of such.*

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**Table 48: Subjects Requiring Treatment for a Gout Flare by Time Interval and Average Post-baseline Serum Urate Level - ITT Subjects**

Time Interval	Serum Urate <6.0 mg/dL		Serum Urate ≥6.0 mg/dL	
	n/N	(%)	n/N	(%)
Screening	61/630	(10%)	32/404	(8%)
Day 1 to Week 28	393/630	(62%)	219/404	(54%)
Day 1 to Week 8	208/630	(33%)	107/404	(26%)
Week 8 to Week 28	307/566	(54%)	176/359	(49%)
Week 8 to Week 12	224/566	(40%)	94/358	(26%)
Week 12 to Week 16	112/537	(21%)	71/334	(21%)
Week 16 to Week 20	79/511	(15%)	59/320	(18%)
Week 20 to Week 24	65/491	(13%)	46/311	(15%)
Week 24 to Week 28	61/483	(13%)	54/303	(18%)
During Prophylaxis <sup>&amp;</sup>	216/630	(34%)	112/403	(28%)
After Prophylaxis <sup>&amp;</sup>	302/630	(48%)	173/403	(43%)

Note: The numerator is the number of subjects requiring treatment for a gout flare in the time interval and treatment group being summarized. The denominator is the number of subjects exposed to at least 1 dose of that treatment in the time interval being summarized.

& Based on each subject's actual prophylaxis period; denominator is the number of subjects with at least 1 prophylactic dose

Cross-reference: Statistical Tables 14.2.2.12 and 14.2.2.13 and Appendices 16.2-6.1.1 and 16.2-6.2

*Reviewers comments: interestingly the rate of attacks appears to slowly decrease in either category. It is possible that even lowering urate modestly in the serum urate ≥6 mg/dl may account for fewer attacks (numbers of attacks drops in both treatment groups).*

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**Table 49 : Subjects Requiring Treatment for a Gout Flare by Time Interval - ITT Subjects with Tophus Present at Baseline**

Time Interval	Placebo		Febuxostat 80 mg QD		Febuxostat 120 mg QD		Febuxostat 240 mg QD		Allopurinol 300/100 mg QD	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
Screening	3/30	(10%)	4/46	(9%)	8/56	(14%)	3/26	(12%)	8/65	(12%)
Day 1 to Week 28	20/30	(67%)	29/46	(63%)	41/56	(73%)	19/26	(73%)	38/65	(58%)
Day 1 to Week 8	9/30	(30%)	13/46	(28%) <sup>m</sup>	28/56	(50%) <sup>a</sup>	12/26	(46%)	17/65	(26%)
Week 8 to Week 28	18/24	(75%)	25/37	(68%)	33/48	(69%)	14/22	(64%)	29/54	(54%)
Week 8 to Week 12	10/24	(42%)	16/37	(43%)	25/48	(52%)	12/22	(55%)	12/54	(22%)
Week 12 to Week 16	10/24	(42%)	10/35	(29%)	15/46	(33%)	5/21	(24%)	16/50	(32%)
Week 16 to Week 20	6/24	(25%)	8/31	(26%)	9/43	(21%)	2/20	(10%)	9/50	(18%)
Week 20 to Week 24	6/23	(26%)	5/31	(16%)	9/40	(23%)	1/19	(5%)	7/48	(15%)
Week 24 to Week 28	6/22	(27%)	6/30	(20%)	8/39	(21%)	1/18	(6%)	7/48	(15%)
During Prophylaxis <sup>&amp;</sup>	9/30	(30%)	13/46	(28%) <sup>m</sup>	30/56	(54%) <sup>p,a</sup>	11/26	(42%)	19/65	(29%)
After Prophylaxis <sup>&amp;</sup>	18/30	(60%)	25/46	(54%)	33/56	(59%)	14/26	(54%)	29/65	(45%)

Comparisons between treatment groups were made with a CMH test stratified by baseline renal function (serum creatinine  $\leq 1.5$  mg/dL vs.  $>1.5$  mg/dL).

Note: The numerator is the number of subjects requiring treatment for a gout flare in the time interval and treatment group being summarized. The denominator is the number of subjects exposed to at least 1 dose of that treatment in the time interval being summarized.

p Statistically significant difference versus placebo ( $p \leq 0.05$ )

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

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

& Based on each subject's actual prophylaxis period; denominator is the number of subjects with at least 1 prophylactic dose

Cross-reference: Statistical Table 14.2.2.14 and Appendices 16.2-6.2 and 16.2-6.3.1

*Reviewers comments: the rate of attacks is again lowest in the febuxostat 240 mg group followed by allopurinol.*

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Finally, in regards to gouty flares the sponsor was requested to provide a Kaplan-Meier analysis of time to (first) flare following the period of prophylaxis. In addition, the sponsor provided a K-M analysis of time to last flare based on the reasoning that reduction in serum urate levels chronically would eventually result in a shorter time to last flare and a longer event free interval. Both analyses are provided below.

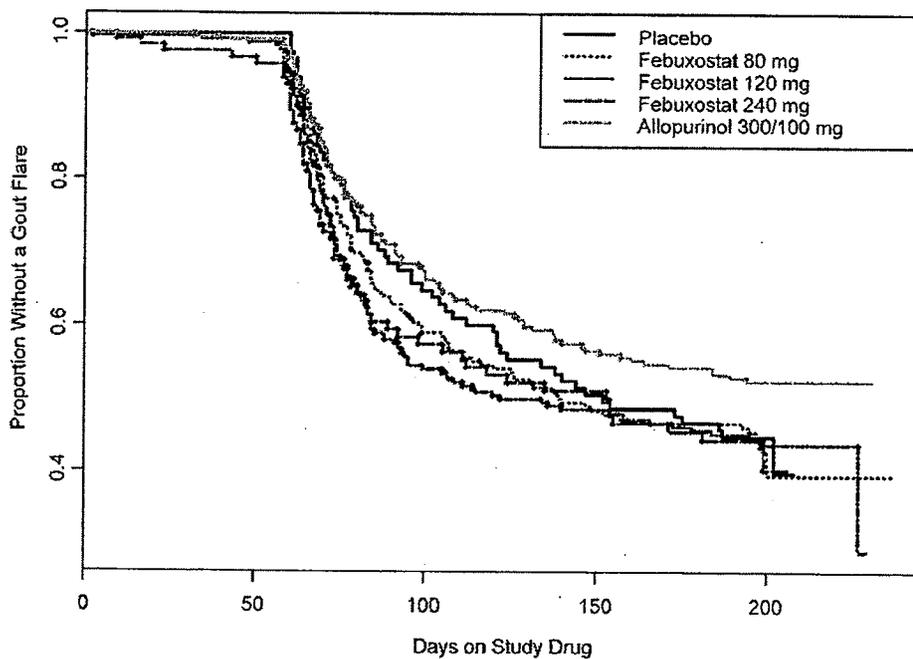
**Table 50: Time to First Post-Prophylaxis Gout Flare Kaplan-Meier Point Estimates and Test for Equality**

Treatment group	Mean (days)		Median (days)			p-value
	Mean	Std. Error	Median	Lower	Upper	
Placebo	143.7	5.60	152	120	--	0.1428
Febuxostat 80 mg QD	138.7	4.14	139	107	200	
Febuxostat 120 mg QD	146.8	4.97	122	93	--	
Febuxostat 240 mg QD	134.7	6.19	153	92	--	
Allopurinol 300/100 mg/QD	145.4	3.71	--	151	--	

CI=Confidence Interval

Note: -- indicates inability to estimate value based on these data.

**Figure 3: Kaplan-Meier Function Estimates for Time to First Post-Prophylaxis Gout Flare**



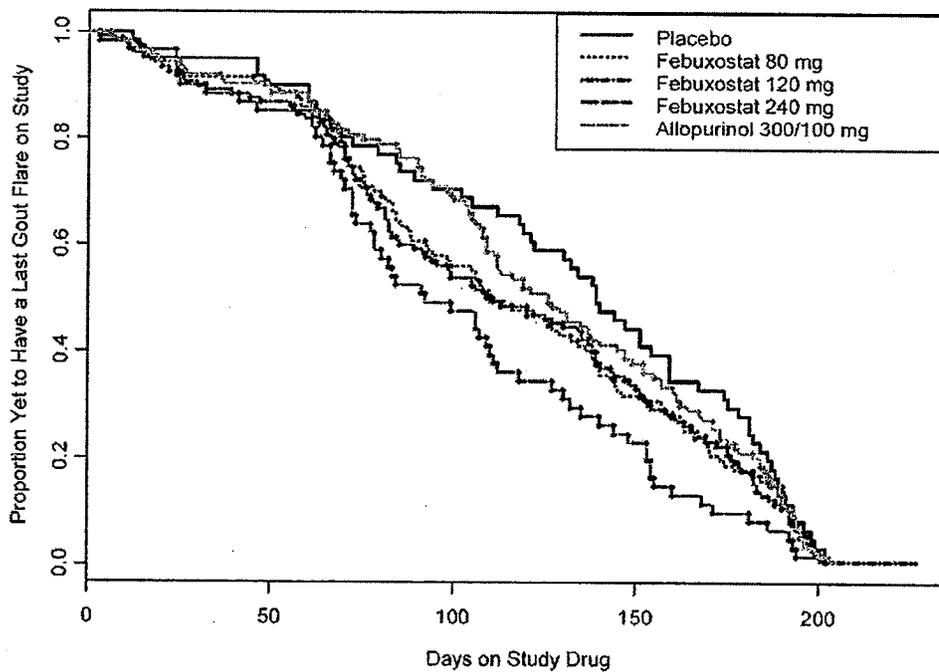
**Table 51 : Time to Last Gout Flare Kaplan-Meier Point Estimates and Test for Equality**

Treatment group	Mean (days)		Median (days)			p-value
	Mean	Std. Error	Median	95% CI		
				Lower	Upper	
Placebo	130.8	7.00	139	121	159	0.0378
Febuxostat 80 mg QD	115.9	5.35	111	93	136	
Febuxostat 120 mg QD	114.6	5.01	110	91	138	
Febuxostat 240 mg QD	101.6	6.53	92	78	111	
Allopurinol 300/100 mg/QD	124.1	5.08	126	109	145	

CI=Confidence Interval

Note: -- indicates inability to estimate value based on these data.

**Figure 4: Kaplan-Meier Function Estimates for Time to Last Gout Flare**



*Reviewer comments: The time to flare analysis does not demonstrate a difference between treatment groups. However, the time to last flare suggests that at the highest dose (240 mg, a dose that is not requested for labeling) that the time to last flare is shorter than the other*

Clinical Review  
{Schiffenbauer, Joel}  
{NDA 21-856}  
{Uloric/febuxostat}

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*treatment groups. Whether the results for the lower doses (80 and 120 mg) would eventually result in a similar finding is not known at this time. These are all post-hoc analyses.*

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The next set of table provide data on analyses of patient reported outcomes. This has not been examined previously in gout.

**Table 52 : Mean Change from Baseline in SF-36™ Health Survey at the Week 28 and Final Visits - ITT Subjects**

Area Domain	Placebo		Febuxostat 80 mg QD		Febuxostat 120 mg QD		Febuxostat 240 mg QD		Allopurinol 300/100 mg QD		
	Timepoint	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
<b>Functional Status</b>											
<b>Physical Functioning</b>											
Baseline	130	73.1 (27.48)	257	76.5 (25.58)	262	76.7 (24.59)	132	77.1 (20.63)	263	78.2 (22.43)	
Δ at Week 28	97	4.7 <sup>‡</sup> (19.45)	151	1.6 (18.29)	178	1.9 (22.93)	82	1.5 (17.14)	196	0.5 (18.51)	
Δ at Final	112	4.2 <sup>‡</sup> (18.85)	193	-0.6 <sup>‡</sup> (20.30)	213	1.0 (21.59)	110	-0.8 (17.63)	227	0.1 (17.96)	
<b>Role-Physical</b>											
Baseline	130	65.6 (40.97)	256	64.1 (42.55)	261	68.9 (40.02)	132	68.6 (38.66)	263	71.8 (39.40)	
Δ at Week 28	97	3.3 (37.66)	151	15.8 <sup>‡p</sup> (39.24)	178	8.0 <sup>‡</sup> (42.13)	82	17.4 <sup>‡p</sup> (45.42)	196	7.9 <sup>‡</sup> (41.54)	
Δ at Final	112	2.8 (37.68)	193	9.6 <sup>‡</sup> (40.75)	212	2.8 (44.05)	110	4.1 (51.86)	227	5.4 (43.00)	
<b>Bodily Pain</b>											
Baseline	130	53.7 (27.46)	257	57.4 (26.58)	262	56.1 (25.83)	131	56.4 (24.54)	263	60.4 (24.13)	
Δ at Week 28	97	7.0 <sup>‡</sup> (28.18)	152	11.9 <sup>‡</sup> (26.79)	176	11.3 <sup>‡</sup> (26.04)	81	13.7 <sup>‡</sup> (27.31)	196	8.7 <sup>‡</sup> (25.99)	
Δ at Final	112	6.2 <sup>‡</sup> (27.70)	194	6.5 <sup>‡</sup> (28.81)	211	6.9 <sup>‡</sup> (28.15)	109	7.9 <sup>‡</sup> (31.65)	227	7.6 <sup>‡</sup> (25.92)	
<b>General Health</b>											
Baseline	130	67.2 (20.28)	257	66.6 (21.30)	262	69.1 (19.10)	132	67.9 (16.77)	263	70.5 (18.08)	
Δ at Week 28	97	0.6 (12.85)	152	2.4 <sup>‡</sup> (13.75)	178	2.3 <sup>‡</sup> (15.08)	82	1.4 (12.86)	195	2.1 <sup>‡</sup> (13.34)	
Δ at Final	112	0.0 (13.14)	194	0.8 (14.63)	213	1.5 (15.04)	110	-0.4 (14.02)	226	1.3 (13.48)	
<b>Vitality</b>											
Baseline	130	59.6 (21.28)	257	58.7 (22.12)	262	59.2 (20.57)	131	61.0 (18.00)	263	62.8 (18.99)	
Δ at Week 28	97	5.4 <sup>‡</sup> (14.55)	152	2.5 <sup>‡</sup> (14.34)	177	4.5 <sup>‡</sup> (16.60)	81	1.5 (14.97)	196	3.1 <sup>‡</sup> (15.09)	
Δ at Final	112	3.3 <sup>‡</sup> (15.20)	194	1.3 (14.98)	212	2.3 (18.75)	109	-0.4 (16.13)	227	1.8 (15.32)	
<b>Social Functioning</b>											
Baseline	130	78.3 (25.22)	257	80.9 (24.16)	262	81.7 (23.74)	132	84.6 (20.01)	263	84.9 (20.31)	
Δ at Week 28	97	4.9 <sup>‡</sup> (20.30)	152	3.7 <sup>‡</sup> (20.08)	178	5.0 <sup>‡</sup> (21.89)	82	4.6 (22.61)	196	2.3 (18.38)	
Δ at Final	112	4.2 <sup>‡</sup> (20.38)	194	0.1 (23.20)	213	1.1 (24.81)	110	-0.7 (26.49)	227	0.9 (19.44)	
<b>Role-Emotional</b>											
Baseline	130	80.8 (35.91)	256	81.2 (34.66)	260	82.6 (32.54)	132	84.1 (29.83)	263	85.7 (28.91)	
Δ at Week 28	97	0.3 (36.16)	151	2.6 (30.68)	178	6.7 <sup>‡</sup> (32.16)	81	2.9 (28.48)	196	1.8 (29.69)	
Δ at Final	112	-0.3 (38.10)	193	1.4 (31.88)	211	1.3 (36.06)	109	-0.3 (33.79)	226	-0.4 (31.29)	
<b>Mental Health</b>											
Baseline	130	76.8 (17.74)	257	77.8 (15.79)	262	78.7 (18.26)	131	80.6 (14.15)	263	79.8 (15.26)	
Δ at Week 28	97	2.9 <sup>‡</sup> (12.64)	152	1.6 (11.76)	177	2.2 <sup>‡</sup> (11.33)	81	-0.1 (11.47)	196	0.9 (12.07)	
Δ at Final	112	2.4 (13.41)	194	0.4 (13.05)	212	0.7 (12.43)	109	-1.0 <sup>‡</sup> (12.17)	227	0.7 (12.35)	
<b>Reported Health Transition</b>											
Baseline	129	55.2 (20.65)	257	54.3 (20.87)	260	53.7 (19.80)	132	53.8 (17.61)	263	54.2 (17.79)	
Δ at Week 28	93	3.5 (26.48)	152	8.9 <sup>‡</sup> (24.82)	177	8.8 <sup>‡</sup> (27.20)	82	11.6 <sup>‡p</sup> (24.59)	194	7.2 <sup>‡</sup> (23.17)	
Δ at Final	108	1.4 (27.94)	193	6.6 <sup>‡</sup> (24.57)	210	7.6 <sup>‡p</sup> (26.82)	110	7.5 <sup>‡</sup> (23.84)	225	6.1 <sup>‡</sup> (23.00)	

All scores are on a 0-100 scale with higher scores indicating better health.

Positive change from baseline indicates improvement.

‡ Statistically significant within group change from baseline (p≤0.05) using a paired t-test

p Statistically significant difference versus placebo (p≤0.05) using two-way ANOVA with treatment and baseline renal function (serum creatinine ≤1.5 mg/dL vs. >1.5 mg/dL) as factors

Cross-reference: Statistical Table 14.2.2.19 and Appendices 16.2-6.4.1 through 16.2-6.4.9

APPEARS THIS WAY  
 ON ORIGINAL

**Table 53 : Mean Change from Baseline in SF-36™ Health Survey at the Week 28 and Final Visits - ITT  
 Subjects: Physical and Mental component summary**

Area Domain	Placebo		Febuxostat 80 mg QD		Febuxostat 120 mg QD		Febuxostat 240 mg QD		Allopurinol 300/100 mg QD	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
<b>Functional Status</b>										
<b>Physical Component Summary</b>										
Baseline	130	44.4 (10.90)	256	45.2 (10.60)	260	45.7 (9.74)	131	45.3 (9.20)	262	46.6 (9.22)
Δ at Week 28	97	1.9 <sup>‡</sup> (8.17)	150	3.3 <sup>‡</sup> (7.71)	176	2.4 <sup>‡</sup> (8.84)	81	3.9 <sup>‡</sup> (8.81)	195	2.2 <sup>‡</sup> (8.28)
Δ at Final	112	1.6 <sup>‡</sup> (8.02)	192	1.6 <sup>‡</sup> (8.70)	209	1.5 <sup>‡</sup> (9.07)	109	1.4 (9.97)	225	1.7 <sup>‡</sup> (8.42)
<b>Mental Component Summary</b>										
Baseline	130	51.9 (10.46)	256	52.0 (9.30)	260	52.5 (9.79)	131	53.7 (8.09)	262	53.5 (8.49)
Δ at Week 28	97	1.1 (7.92)	150	0.4 (7.11)	176	1.7 <sup>‡</sup> (7.10)	81	-0.2 (7.00)	195	0.4 (6.63)
Δ at Final	112	0.7 (8.57)	192	-0.1 (8.04)	209	0.3 (8.40)	109	-0.8 (8.15)	225	-0.1 (7.12)

All scores are on a 0-100 scale with higher scores indicating better health.

Positive change from baseline indicates improvement.

‡ Statistically significant within group change from baseline (p≤0.05) using a paired t-test

p Statistically significant difference versus placebo (p≤0.05) using two-way ANOVA with treatment and baseline renal function (serum creatinine ≤1.5 mg/dL vs. >1.5 mg/dL) as factors

Cross-reference: Statistical Table 14.2.2.19 and Appendices 16.2-6.4.1 through 16.2-6.4.9

*Reviewers comments: the key results here are that placebo looks better than any of the treatment groups. In the short term this may not be surprising if treatment leads to an increase rate of clinical gout attacks. Subjects may feel they are doing worse in the short term due to an increase in gouty flares. It would be interesting to follow this up in the long term with repeat measures.*

**Table 54: Mean Change from Baseline in MOS Health Distress at the Week 28 and Final Visits - ITT  
 Subjects**

APPEARS THIS WAY  
 ON ORIGINAL

Clinical Review  
 {Schiffenbauer, Joel}  
 {NDA 21-856}  
 {Uloric/febuxostat}

Area Domain	Placebo		Febuxostat 80 mg QD		Febuxostat 120 mg QD		Febuxostat 240 mg QD		Allopurinol 300/100 mg QD	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
<b>Health Distress</b>										
Baseline	130	74.4 (27.10)	256	74.9 (26.06)	262	77.9 (24.64)	132	79.4 (22.21)	262	81.3 (19.80)
Δ at Week 28	97	4.4 <sup>‡</sup> (16.69)	150	7.8 <sup>‡a</sup> (20.15)	178	6.2 <sup>‡</sup> (18.44)	82	7.9 <sup>‡</sup> (18.50)	194	3.8 <sup>‡</sup> (18.55)
Δ at Final	112	4.1 <sup>‡</sup> (16.46)	192	3.4 <sup>‡</sup> (21.99)	213	2.6 (20.99)	110	2.7 (20.99)	225	2.7 <sup>‡</sup> (18.37)

All scores are on a 0-100 scale with higher scores indicating better health.

Positive change from baseline indicates improvement.

‡ Statistically significant within group change from baseline ( $p \leq 0.05$ ) using a paired t-test

a Statistically significant difference versus allopurinol 300/100 mg QD ( $p \leq 0.05$ ) using two-way ANOVA with treatment and baseline renal function (serum creatinine  $\leq 1.5$  mg/dL vs.  $> 1.5$  mg/dL) as factors

Cross-reference: Statistical Table 14.2.2.19 and Appendix 16.2-6.4.10

*Reviewers comments: results here confirm the results with the SF-36.*

#### 4.4 Safety

See safety review by Dr. T. Oussova

#### 4.5 Conclusions

There is provided evidence of the efficacy of febuxostat 80, 120 and 240 mg in lowering serum urate levels. The evidence appears to indicate that each of these doses is superior to allopurinol in this effect. However, the effects on the rate of gouty flares is not conclusively demonstrated. In addition, the adequacy of the allopurinol in terms of potency needs to be addressed.

### 10.1.2 Trial 010

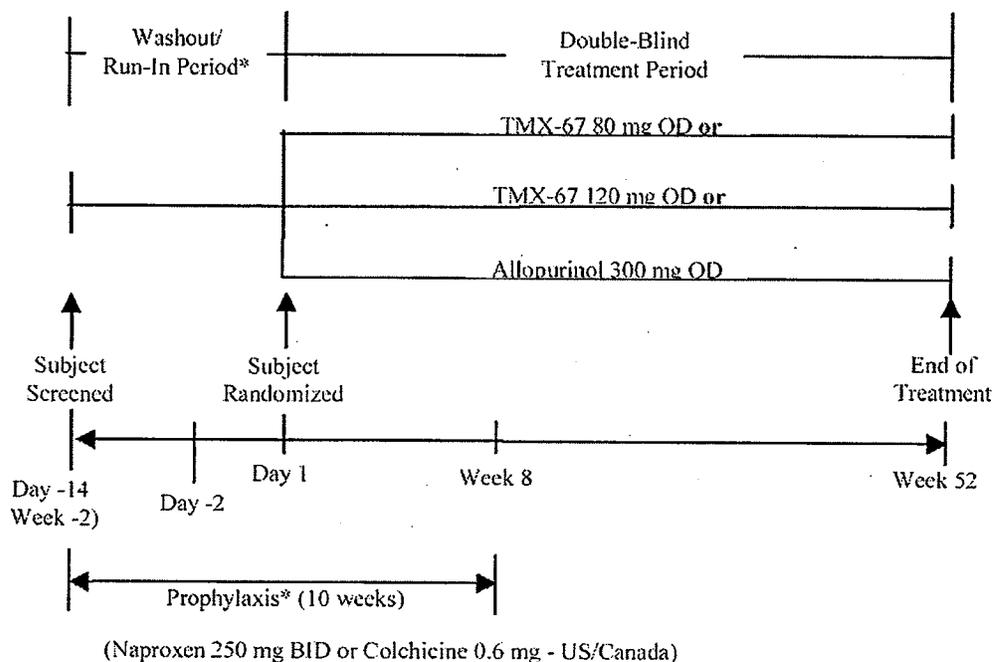
The objective of this study was to compare the safety and efficacy of febuxostat versus allopurinol in subjects with gout (no placebo group was included in this trial).

#### 1. Protocol

This was a Phase 3, multicenter, randomized, double-blind, parallel-design, 3-arm study designed to compare the safety and efficacy of febuxostat versus allopurinol in subjects with gout. The study consisted of a Screening Visit (Day -14 for subjects who were taking allopurinol or uricosuric agents prior to the study and between Day -14 and Day -3 for subjects who were not taking such agents prior to the study), a Day -2 Visit, and a Day 1 Visit, followed by a 52-week Double-blind Treatment Period.

A schematic of the study design is provided in Figure below.

Figure 5: study design



\* Subjects who were not receiving allopurinol or uricosuric agents prior to study will begin treatment with naproxen or colchicine at the Day 1 Visit; these subjects will not be required to complete a 14-day Washout/Run-In period prior to randomization; however, they will be required to complete all screening and Day -2 procedures. For subjects who do not require a washout, the Screening Visit can occur anytime between Day -14 and Day -3.

This study was intended to be used as a Pivotal Phase 3 study to support an indication for the management of hyperuricemia in patients with gout.

This study was designed to compare febuxostat to allopurinol; the primary efficacy variable was the proportion of subjects whose last 3 serum urate levels were <6.0 mg/dL.

The febuxostat 80 mg QD and 120 mg QD treatment groups were compared to the allopurinol 300 mg QD treatment group to establish the efficacy of febuxostat versus an active control. The allopurinol 300 mg QD dose was selected based on the most commonly used dose in treatment of gout and on dosing information included in the allopurinol package insert.

Subjects were treated prophylactically with either naproxen 250 mg BID or colchicine 0.6 mg QD for the first 8 weeks of the 52-week Double-blind Treatment Period, as well as for 2 weeks during the Screening Period for subjects who discontinued allopurinol or uricosuric agents at the Screening Visit. Both naproxen and colchicine are indicated for the treatment of acute gouty arthritis.

A non-inferiority margin of 10% and an allopurinol response rate of 60% were discussed and agreed upon with the DAAODP in the End-of-Phase 2 meeting and in subsequent discussions and correspondence. In addition, the primary endpoint used in the study, the proportion of subjects with the last three serum urate measurements <6.0 mg/dL, was also discussed and agreed upon with the DAAODP.

### **Inclusion Criteria**

#### **Inclusion Criteria at Screening (Day -14)**

1. Subjects were male or female, 18 to 85 years of age, inclusive.
2. Females were either post-menopausal for at least 2 years, surgically sterile (including bilateral tubal ligation) or using a medically accepted means of contraception. Subjects were allowed to continue a stable regimen of at least 3 months of oral contraceptives or could have had injectable contraceptives administered within the previous 3 months. Subjects were to use an additional barrier method of birth control during the course of the study and for 30 days after the discontinuation of study drug. Subjects could have used a double-barrier method of birth control (eg, condom plus spermicide; cervical cap plus spermicide; or diaphragm plus spermicide). Subjects were to use the double-barrier method of birth control during the course of the study and for 30 days after discontinuation of study drug. Females were required to have a negative serum pregnancy test at Screening.
3. Subjects had a history or presence of gout as defined by the preliminary criteria of the American Rheumatism Association (ARA) for the classification of the acute arthritis of primary gout.
  - ~ the presence of characteristic urate crystals in the joint fluid and/or
  - ~ a tophus proven to contain urate crystals by chemical or polarized light microscopic means and/or
  - ~ the presence 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. Subjects had normal renal function defined as:

a serum creatinine level  $<1.5$  mg/dL or  $<133$   $\mu\text{mol/L}$  on the Day -14  
— central laboratory testing

b(4)

an estimated creatinine clearance of  $>50$  mL/minute or  $>0.83$  mL/second reported by — central laboratory based on the Day -14 serum creatinine test result

estimated creatinine clearance could have been calculated according to the following Cockcroft-Gault formula:

Estimated creatinine clearance in mL/min for males:

$(140 - \text{age in years}) (\text{weight in kg})$

$72 (\text{serum creatinine in mg/dL})$

for females: multiply above calculation by 0.85

If the investigator felt the estimated creatinine clearance result did not reflect the subject's true renal function, upon approval from TAP, a measured 24-hour creatinine clearance test was performed by —. If the serum creatinine was  $\leq 1.5$  mg/dL or  $\leq 133$   $\mu\text{mol/L}$  and the measured 24-hour creatinine clearance was  $\geq 50$  mL/minute, this inclusion criterion was satisfied.

#### **Inclusion Criteria at Day -2**

1. Subjects had hyperuricemia defined as a serum urate level  $\geq 8.0$  mg/dL. Serum urate levels were based on the laboratory result received from the central laboratory.
2. Subjects continued to meet all inclusion and exclusion criteria.

#### **Exclusion Criteria at Screening (Day -14)**

1. Female subjects who were breast-feeding or pregnant.
2. Subjects with a history of xanthinuria.
3. Subjects who were on concomitant therapy with any systemic or topical medications, prescribed or nonprescribed, containing aspirin or other salicylates at the Screening Visit. Stable, low doses of aspirin were allowed.
4. Subjects on thiazide diuretic therapy.
5. Subjects receiving  $>10$  mg/day of prednisone. Stable doses ( $<10$  mg/day), as well as inhaled and intranasal steroids were allowed.
6. Female subjects who had a change in hormone replacement therapy or oral contraceptive therapy within 3 months of Screening.
7. Subjects whose alcohol intake was  $>14$  drinks/week. Alcohol abuse within 5 years or current excessive alcohol use was prohibited.
8. Subjects on any concomitant urate-lowering therapy.
9. Subjects with active liver disease or hepatic dysfunction (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]  $>1.5$  times the upper limit of normal).
10. Subjects with any other significant medical condition as defined by the investigator that would have interfered with the treatment, safety, or compliance

with the protocol (eg, a clinically significant ECG result).

11. Subjects with a serum urate level <8.0 mg/dL who were not taking uric acid-lowering therapy.
12. Subjects who had previously participated in a clinical study with febuxostat.
13. Subjects intolerant to allopurinol.
14. Subjects were not to receive naproxen if they had a history of hypersensitivity to naproxen or any other NSAID, active gastric ulcer disease, or a history of recent gastrointestinal intolerance with bleeding due to naproxen or any other NSAID.
15. Subjects were not to receive colchicine if they had a history of hypersensitivity to colchicine.
16. Subjects with a history of cancer (other than basal cell carcinoma of the skin) within 5 years prior to the Screening Visit or subjects who had taken any systemic cancer chemotherapy within 5 years prior to the Screening Visit.
17. Subjects who had active rheumatoid arthritis and were required to take medication for the treatment of their rheumatoid arthritis (subjects receiving only prednisone <10 mg QD were allowed).

### Randomization

— provided an IVRS for the study. Each site was provided with instructions and training on the use of this system. Sites called the system to randomize a subject to a treatment group on Day 1 and to receive subsequent drug carton assignments at each study visit.

b(4)

Double-blind study drug, once assigned, was not to be reassigned to another subject. If a subject discontinued from the study after randomization, the used or unused study drug carton containing the 2 bottles of study drug was to be returned to \_\_\_\_\_ for destruction.

b(4)

The randomization schedule was computer-generated by the TAP Statistics Department. The randomization code was maintained in a locked, confidential location until the time of unblinding by a TAP statistician.

The study drug assignment for each subject was available to the investigator via a scratch-off label located on the study drug carton on the portion of the label that was retained by the site (for placement on the CRF) prior to dispensing the study drug to the subject. The blind could have been accessed via the scratch-off label if, in the opinion of the investigator, it was in the subject's best interest for the physician to know the study drug assignment. The investigator was to notify the sponsor before breaking the blind, unless identification of the study drug was required for emergency therapeutic measures. In the latter case, the sponsor was to be notified within 24 hours of the blind being broken. The date, time, and reason that the blind was broken were to be recorded on the appropriate CRF.

### Blinding

Combinations of febuxostat 20 mg tablets to achieve febuxostat 80 mg or 60 mg doses were overencapsulated to assure blinding. Each febuxostat 20 mg tablet contained 20 mg of febuxostat (TEI-6720), monohydrate lactose, microcrystalline cellulose \_\_\_\_\_, hydroxypropyl cellulose, croscarmellose sodium, silicon dioxide, magnesium stearate, \_\_\_\_\_ and opadry II green. The appropriate number of febuxostat tablets (three 20 mg tablets to achieve 60 mg febuxostat or four 20 mg tablets to achieve 80 mg febuxostat) were placed in an iron gray opaque (No. 00) gelatin capsule along with a \_\_\_\_\_ filler. Two capsules containing 60 mg febuxostat each were administered to achieve the febuxostat 120 mg dose. One capsule containing 80 mg febuxostat and a placebo capsule were administered to achieve the febuxostat 80 mg dose.

b(4)

Allopurinol \_\_\_\_\_ 300 mg tablets were purchased from \_\_\_\_\_ for this study in their marketed containers. Each allopurinol 300 mg tablet was overencapsulated in an iron gray opaque (No. 00) gelatin capsule along with a \_\_\_\_\_ filler. Placebo capsules contained \_\_\_\_\_ filler in an iron gray opaque (No. 00) gelatin capsule.

b(4)

Dissolution profiles for the overencapsulated (blinded) products were compared to those of the unblinded products. In the case of the 60 and 80 mg febuxostat capsules, dissolution profiles for the capsules were compared to those of three 20 mg tablets (for the 60 mg capsules) and four 20-mg tablets (for the 80 mg capsules), respectively. For the blinded allopurinol capsules, dissolution profile was compared to 300 mg allopurinol tablet profile. Dissolution profiles for all blinded products were similar to those of unblinded products for febuxostat and allopurinol. Stability studies were conducted to ensure that assay and dissolution profiles of the overencapsulated products did not change over the duration of the clinical study.

*Reviewers comments: as discussed under trial 009, the issue is whether the allopurinol used as the comparator retained full potency and was therefore an adequate comparator. This is critical in this trial because there is no placebo control. Conclusions as to the relative efficacy of febuxostat, therefore rely entirely on comparisons to allopurinol and any claims of superiority must be based on valid comparisons.*

### **Concomitant medications**

Subjects were to refrain from taking any medication for the purpose of lowering serum urate levels. Subjects who were taking any of the excluded medications listed below could have entered the study if they were washed off the excluded medication for a minimum of 5 half-lives prior to the Day 1 Randomization Visit.

The following medications were not to be taken during the study: allopurinol (unless the subject was randomized to it), azathioprine, meclofenamate, mercaptopurine, chronic use of NSAIDs, salicylate-containing medications (eg, Alka-Seltzer), sulfinpyrazone, trimethoprim-sulfamethoxazole (eg, Bactrim and Septra), uricosurics (probenecid and

combination), benzbromarone, losartan potassium (Cozaar), cyclophosphamide, thiazide diuretics, valsartan/hydrochlorothiazide (Diovan HCT), pyrazinamide, methotrexate, intravenous colchicine, and prednisone >10 mg/day.

Subjects were allowed to take the following medications during the study, but they must have been stable, low doses: ascorbic acid citrate (ie, <500 mg/day), low-dose aspirin (ie, <325 mg/day), citrate (ie, <500 mg/day), nicotinic acid (ie, <500 mg/day), and prednisone (ie, <10 mg/day).

The following medications were allowed on an as needed basis only: acetaminophen, nonsalicylate NSAIDs, and glyceryl guaiacolate. If required more frequently, sites were to contact TAP for approval.

*Reviewers comments: these are similar to those for study 009.*

### **Efficacy assessments**

Efficacy of the study drug was assessed using serum urate levels, physical assessment of tophus, and gout flares. Prior to Amendment No. 2, x-ray and MRI for tophus were performed in a subset of subjects at selected sites. The imaging portion of the study was discontinued due to enrollment being met and only a small number of tophi subjects having been imaged. No further imaging procedures, x-ray and MRI, were performed. The safety of study drug was assessed throughout the study by monitoring adverse events, laboratory tests, physical examinations, concomitant medication use, vital signs, and ECG results.

**Table 55 : Schedule of Assessments**

**APPEARS THIS WAY  
ON ORIGINAL**

Clinical Review  
 {Schiffenbauer, Joel}  
 {NDA 21-856}  
 {Uloric/febuxostat}

APPEARS THIS WAY  
ON ORIGINAL

PROCEDURE	Washout/ Run-in Period		52-week Double-blind Treatment Period															
	Day -14	Day -2	Day 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52*	
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17	
Informed consent	X																	
Medical, social history & height	X																	
Complete physical exam		X					X			X			X					X
Update medical history			X															
Brief physical exam	X		X		X	X		X	X		X	X		X	X	X		
ECG		X								X								X
Weight and vitals	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality-of-life questionnaires			X							X								X
Tophus physical assessment <sup>a</sup>	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Imaging for tophi subset <sup>b</sup>			X							X								X
<b>Blood Tests</b>																		
Chemistry tests <sup>c</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum urate levels <sup>d</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation <sup>e</sup>	X		X				X			X			X					X
Hematology tests <sup>f</sup>	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Thyroid function tests <sup>g</sup>	X		X							X								X
Serum pregnancy test <sup>h</sup>	X	X						X										X

- a Or at Premature Discontinuation.
- b For subjects with palpable tophi present.
- c Procedure not applicable after Amendment No. 2.
- d Chemistry tests included fasting glucose, total cholesterol, triglycerides, total protein, albumin, total bilirubin, amylase, SGOT, SGPT, alkaline phosphatase, LDH, BUN, creatinine, magnesium, sodium, potassium, chloride, bicarbonate, phosphorus, and calcium.
- e Measured by enzymatic method as part of the chemistry panel. All serum urate levels were blinded to the subject, investigator and staff, and sponsor beginning at the Day 1 Visit.
- f Coagulation tests included PT and PTT.
- g Hematology tests included RBC count, WBC count, total and differential, platelet count, hemoglobin, hematocrit, MCV, MCH, MCHC, and reticulocyte count.
- h Thyroid tests included thyroid stimulating hormone (TSH), triiodothyronine (T<sub>3</sub>), thyroxine (T<sub>4</sub>), and free thyroxine (Free T<sub>4</sub>).
- i A serum pregnancy test was performed at the Screening Visit (Day -14), Day -2, Weeks 12, 24, 36 and 52 for female subjects of childbearing potential. In addition, all other female subjects participating in the study had a serum pregnancy test performed at the Screening Visit (Day -14) and the end of study visit (Week 52).
- j Urinalysis included a determination of specific gravity, pH, protein, ketones, nitrite, glucose and a microscopic evaluation for WBCs, RBC, casts, and crystals.
- k A urine pregnancy test was required for all female subjects on Day 1.
- l Subjects who were taking alloprinozol or uricosuric agents prior to the study were dispensed naproxen or colchicine at the Day -14 and Week 4 Visits. Subjects who were not receiving alloprinozol or uricosuric agents prior to the study were dispensed naproxen or colchicine at the Day 1 and Week 4 Visits.

PROCEDURE	Washout/ Run-in Period		52-week Double-blind Treatment Period															
	Day -14	Day -2	Day 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52*	
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16	Visit 17	
Urine tests																		
Urinalysis with microscopy <sup>a</sup>	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test <sup>b</sup>			X															
Adverse event assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE-Rash Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Gout Flare Assessment (if applicable)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant med assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense naproxen or colchicine <sup>c</sup>	X		X		X													
Collect missed naproxen or colchicine					X	X												
Dispense study drug			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug compliance			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Discuss open-label extension study																		X

- a Or at Premature Discontinuation.
- b For subjects with palpable tophi present.
- c Procedure not applicable after Amendment No. 2.
- d Chemistry tests included fasting glucose, total cholesterol, triglycerides, total protein, albumin, total bilirubin, amylase, SGOT, SGPT, alkaline phosphatase, LDH, BUN, creatinine, magnesium, sodium, potassium, chloride, bicarbonate, phosphorus, and calcium.
- e Measured by enzymatic method as part of the chemistry panel. All serum urate levels were blinded to the subject, investigator and staff, and sponsor beginning at the Day 1 Visit.
- f Coagulation tests included PT and PTT.
- g Hematology tests included RBC count, WBC count, total and differential, platelet count, hemoglobin, hematocrit, MCV, MCH, MCHC, and reticulocyte count.
- h Thyroid tests included thyroid stimulating hormone (TSH), triiodothyronine (T<sub>3</sub>), thyroxine (T<sub>4</sub>), and free thyroxine (Free T<sub>4</sub>).
- i A serum pregnancy test was performed at the Screening Visit (Day -14), Day -2, Weeks 12, 24, 36 and 52 for female subjects of childbearing potential. In addition, all other female subjects participating in the study had a serum pregnancy test performed at the Screening Visit (Day -14) and the end of study visit (Week 52).
- j Urinalysis included a determination of specific gravity, pH, protein, ketones, nitrite, glucose and a microscopic evaluation for WBCs, RBC, casts, and crystals.
- k A urine pregnancy test was required for all female subjects on Day 1.
- l Subjects who were taking alloprinozol or uricosuric agents prior to the study were dispensed naproxen or colchicine at the Day -14 and Week 4 Visits. Subjects who were not receiving alloprinozol or uricosuric agents prior to the study were dispensed naproxen or colchicine at the Day 1 and Week 4 Visits.

### **Efficacy Variables**

#### **Primary Variable**

The primary variable was the proportion of subjects whose last 3 serum urate levels were <6.0 mg/dL.

#### **Secondary Variables**

The secondary variables were:

1. The proportion of subjects whose serum urate levels were <6.0 mg/dL.
2. The percent reduction in serum urate levels.
3. The percent reduction in primary tophus size, as determined by physical measurement in the subset of subjects with a primary palpable tophus at the Screening Visit.
4. The reduction in the total number of tophi in the subset of subjects with palpable tophi at the Screening Visit.
5. The proportion of subjects requiring treatment for a gout flare between Weeks 8 and 52 of the 52-week Double-blind Treatment Period.

#### **Data quality**

The CRFs supplied by TAP were used to transmit the information collected during the performance of this study to TAP. Case report forms were to be completed for each subject who received any amount of study drug. The CRFs were reviewed for completeness, legibility, accuracy, and acceptability. A 100% source document review was performed for verifications of data entries on the CRFs. Changes to CRFs that were made subsequent to the investigator's review of the CRFs were made via a Data Clarification/Correction Form.

The Quality Assurance Department of TAP conducted random site audits.

The principal investigator or designee was instructed by the sponsor to retain a copy of all records on file for a period of at least 2 years following: (1) the last approval of the marketing application for an ICH region and until there are no pending or contemplated marketing applications for an ICH region, or (2) the formal discontinuation of the clinical development of the investigational product. The sponsor notified the principal investigator or designee that the documents might be retained for a longer period; if required by the applicable regulatory requirements or by stipulation from TAP. The principal investigator was notified by the sponsor that TAP would inform the investigator or designee, in writing, when records would no longer be retained, or if investigations were discontinued. Collection and interpretation of all imaging procedures (x-ray and pre- and post-contrast MRIs) were assigned to \_\_\_\_\_ a central reading facility.

b(4)

#### **Data Sets Analyzed**

All primary and secondary efficacy analyses were performed on the intent-to-treat (ITT) population, except for the secondary efficacy analyses for the percent reduction in primary tophus size and the reduction in the total number of tophi. The ITT population was defined as all randomized subjects who received at least 1 dose of study drug and

had serum urate levels  $\geq 8.0$  mg/dL at Day -2 as determined by the central laboratory. The analysis for the percent reduction in primary tophus size was performed on the subset of ITT subjects with a primary palpable tophus at baseline. The analysis for the reduction in the total number of tophi was performed on the subset of ITT subjects with palpable tophi at baseline. The last tophus examination obtained prior to the first dose of study drug on Day 1 was used to determine a subject's inclusion in these populations, as well as the baseline primary tophus size and baseline total number of tophi. All randomized subjects who received at least 1 dose of study drug were included in the safety analyses.

### **Study Drug Compliance**

The number of weeks on study drug was summarized by treatment group and overall compliance was determined by taking the difference between the total count of capsules dispensed and returned from both bottles and dividing by the prescribed number of capsules (total number of days on study drug multiplied by 2 capsules per day). Subjects with incomplete capsule counts were assumed to have taken study drug for the calculation of overall compliance. Values  $>100\%$  for overall compliance were set to 100% in the analysis.

### **Efficacy Analyses**

The primary objective of this study was to compare different oral doses of febuxostat to allopurinol. The comparisons for the primary efficacy variable were done sequentially using a closed testing procedure within each of 2 steps.

In the first step, each febuxostat treatment group was compared to the allopurinol treatment group to test for non-inferiority. Each febuxostat treatment group that was shown to be non-inferior to allopurinol was tested for superiority to allopurinol in the second step.

Since the comparisons were done sequentially using a closed testing procedure within each step, adjustments to the overall alpha level were made only within each set of comparisons. In the first step, binomial 97.5% confidence intervals were used to adjust the overall 0.05 level of significance for both comparisons of febuxostat to allopurinol. In the second step, Hochberg's method<sup>31</sup> for multiple comparisons was used to ensure that the overall 0.05 level of significance was maintained for comparisons of each febuxostat treatment group to allopurinol. If only 1 dose group of febuxostat was tested for superiority to allopurinol in the second step, a level of significance of 0.05 was to be used.

### **Primary Efficacy Variable**

The primary efficacy variable was the proportion of subjects whose last 3 serum urate levels were  $<6.0$  mg/dL. After applying the visit windows, each subject's last 3 serum urate levels, regardless of the subject's study completion status, were used to determine the subject's response for the primary efficacy variable. In order to be considered a responder, each

of the last 3 serum urate levels must have been  $<6.0$  mg/dL. If a subject prematurely discontinued from the study before at least 3 serum urate levels were obtained, the subject was considered a nonresponder.

The treatment groups were compared in the following sequential order:

1. Binomial 97.5% confidence intervals, based on the normal approximation for the binomial distribution, were calculated for the differences in response rates between each dose group of febuxostat (80 mg QD and 120 mg QD) and the allopurinol 300 mg QD treatment group. Non-inferiority to allopurinol was declared if the absolute value of the lower bound of the 97.5% confidence interval did not exceed 10%.

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

If both dose groups of febuxostat were compared to allopurinol for superiority in step 2, the p-values from the pairwise comparisons were ordered from smallest to largest and the largest p-value was compared to 0.05. If the largest p-value was less than or equal to 0.05, then both dose groups of febuxostat were considered statistically superior to allopurinol. If the largest p-value was greater than 0.05, then the febuxostat dose group corresponding to that p-value was not considered statistically superior to allopurinol. The second largest p-value was then compared to  $0.05/2=0.025$ . If the second largest p-value was less than or equal to 0.025, then the remaining febuxostat dose group was considered statistically superior to allopurinol. If the second p-value was greater than 0.025, then the remaining febuxostat dose group was not considered statistically superior to allopurinol.

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

An additional analysis of the primary efficacy variable summarized the number and percentage of subjects whose last 3 serum urate levels were  $<6.0$  mg/dL prior to and including the Week 28 visit.

A sensitivity analysis was conducted for the primary efficacy variable by using the available (1 or 2) serum urate levels to determine response for subjects who prematurely discontinued before at least 3 serum urate levels were obtained. This analysis examined the

effect of assigning these subjects as nonresponders in the primary analysis. Subjects without post-baseline serum urate levels were not included in this analysis.

Analyses for the proportion of subjects whose last 3 serum urate levels were <6.0 mg/dL were conducted by age (<45, 45-<65, >65 years), gender (male, female), race (Caucasian, non-Caucasian), baseline BMI (<18.5, 18.5-<25, 25-<30, >30 kg/m<sup>2</sup>), alcohol use (drinkers, non-/ex-drinkers), overall compliance (<80%, 80-<90%, >90%), baseline renal function (normal, impaired), baseline serum urate levels (<9.0, 9.0-<10.0, >10.0 mg/dL), use of previous urate-lowering therapy (prior use, no prior use), baseline palpable tophus presence (tophus present, tophus absent), history of renal calculi (history of calculi, no history of calculi), history of cardiovascular risk factors ( $\geq 1$  risk factor, no risk factors), use of low-dose aspirin (use, no use), baseline calculated creatinine clearance using ideal body weight (<50, 50-<80, 80-<120, >120 mL/min), tobacco use (tobacco user, non-/ex-tobacco user), and metabolic syndrome (subjects with syndrome, subjects without syndrome). Pairwise comparisons between the treatment groups were made with a CMH test adjusting for each factor.

A subject was categorized as having at least 1 cardiovascular risk factor if he had a history of cardiovascular disease, diabetes, hypercholesterolemia, hyperlipidemia, or hypertension.

#### **Secondary Efficacy Variables**

The following secondary efficacy variables were assessed:

1. The proportion of subjects whose serum urate levels were <6.0 mg/dL.
2. The percent reduction in serum urate levels.
3. The percent reduction in primary tophus size, as determined by physical measurement in the subset of subjects with a primary palpable tophus at the Screening Visit.
4. The reduction in the total number of tophi in the subset of subjects with palpable tophi at the Screening Visit.
5. The proportion of subjects requiring treatment for a gout flare between Weeks 8 and 52 of the 52-week Double-blind Treatment Period.

For the secondary efficacy variables, no adjustments for multiple comparisons were performed. Pairwise comparisons were made between the treatment groups.

#### **Determination of Sample Size**

A total of 750 subjects (250 per treatment group) were expected to enroll in this study. The sample size was to provide 1) at least 80% power to meet the non-inferiority criteria between at least 1 febuxostat treatment group and the allopurinol treatment group for the primary efficacy variable based on the assumptions below and 2) at least 90% power to detect a 15% difference between a febuxostat treatment group and the allopurinol treatment group for the primary efficacy variable.

For the determination of non-inferiority between the febuxostat treatment groups and the allopurinol treatment group, the sample size calculation assumed a true response rate of 60% for

the allopurinol treatment group and at least 64% for the febuxostat dose groups, which was based on the TMX-00-004 data and a literature review of historical allopurinol data and in consideration of the differences in expected response rates between the Phase 2 and 3 endpoints. In Study TMX-00-004, a Phase 2, dose-response study in subjects with gout, the proportions of subjects with a serum urate level <6.0 mg/dL after 4 weeks of treatment were 0%, 56%, 76%, and 94% for the placebo, febuxostat 40 mg QD, febuxostat 80 mg QD, and febuxostat 120 mg QD treatment groups, respectively.

## 2. Amendments

### Changes in the Conduct of the Study or Planned Analyses

#### Protocol Changes

There were 3 amendments and 1 site-specific administrative change to the original protocol. Administrative Change No. 1 applied only to those sites that participated in the imaging section of the protocol.

Amendment No. 1, dated 7 August 2002:

- ~ Increased the number of sites from 140 to 160.
- ~ Clarified that European subjects were only to receive TAP-supplied naproxen 250 mg BID as prophylaxis during the period Day -14 through the day before the Week 8 Visit, since the colchicine 0.6 mg dose used in the US and Canada was not customarily used in Europe. From Weeks 8 through 52, European investigators had the option of prescribing commercially available colchicine to treat an acute gout attack. Please note that although European sites had been planned initially, study enrollment was completed before any European sites could be initiated. This was clarified in Amendment 2 to the protocol, as discussed below.
- ~ Clarified the statistical methods for analysis of secondary efficacy endpoints in the synopsis.
- ~ Corrected typographical errors and minor administrative changes to the protocol.
- ~ Clarified various visit windows throughout the protocol.
- ~ Expanded the inclusion criterion regarding normal renal function, such that subjects were to have a serum creatinine level  $\geq 1.5$  mg/dL or  $\geq 137$   $\mu$ mol/L based on the Day -14 laboratory result and an estimated creatinine clearance of  $\geq 50$  mL/minute or  $\geq 0.83$  mL/second reported by based on the Day -14 serum creatinine result. The estimated creatinine clearance may have been calculated according to the Cockcroft-Gault formula.
- ~ Clarified the naproxen hypersensitivity exclusion criterion.
- ~ Clarified that double-blind study drug was ideally to be given in the morning, but that this was not absolutely required.
- ~ Added 2 exclusion criteria: excluding subjects with a history of cancer (other than basal cell carcinoma) within 5 years before Screening and excluding subjects with active rheumatoid arthritis who were using >10 mg prednisone daily.
- ~ Clarified the washout period required for prohibited concomitant medication prior

b(4)

to study entry.

- ~ Clarified that the allopurinol and colchicine package inserts in the protocol reflected the US labeling and that package inserts for Canada and European countries were to be provided within those countries by the clinical monitor.
- ~ Added the excipients/composition of the tablets or capsules to Identity of Investigational Product(s).
- ~ Clarified that the Day -2 blood draw was to be performed for both serum urate and other biochemistry parameters.
- ~ Clarified that the tophi assessment was to be made by the same site personnel (trained on tophi measurement) throughout the study.
- ~ Clarified pregnancy testing for females and procedures that were to be followed if a female subject became pregnant during the study.
- ~ Clarified that all adverse events occurring during the Screening Period and during the study were to be recorded on the appropriate CRF, and that clinically significant adverse events (including SAEs) reported by the subject within 30 days after study completion were also to be recorded on the appropriate CRF.
- ~ Clarified SAE reporting requirements and contact information.
- ~ Clarified determination of sample size.
- ~ Clarified regulatory documents required prior to study initiation at the site.

Administrative Change No. 1, dated 23 October 2002:

- ~ Corrected the following pulse sequences for MRI:
  - 2D T1 weighted Spin Echo pre-contrast with Fat Sat TR/TE 600/<=20
  - 2D T2 Fast Spin Echo pre-contrast with Fat Sat TR/TE >3000/>80, ETL=8
  - 3D T1 Weighted (SPGR) pre-contrast with Fat Sat TR/TE 15-20/<10
  - 3D T1 Weighted (SPGR) post-contrast with Fat Sat TR/TE 15-20/<10
- ~ Added that the post-contrast MRI sequence was to be started 10 minutes after the end of the contrast injection.

Amendment No. 2, dated 19 June 2003:

- ~ Removed all references to European study conduct throughout the protocol due to enrollment being met by the US and Canadian sites.
- ~ Discontinued the imaging portion of the study due to enrollment being met and only a small number of tophi subjects having been imaged.
- ~ Updated the statistical sections to reflect a change in the primary efficacy variable for the study based on the End-of-Phase 2 discussions with the FDA. The primary efficacy variable for this study was changed to the proportion of subjects whose last 3 serum urate levels were <6.0 mg/dL.
- ~ Added Administrative Change No. 1 dated 23 October 2002 as an appendix; however, it was not incorporated into the protocol, as the administrative change only pertained to those sites participating in the imaging portion of the protocol and was no longer applicable.
- ~ Added the elements of the Health Information and Portability Act (HIPAA) authorization as an appendix to the protocol.

~ Incorporated minor grammatical and formatting changes.

Amendment No. 3, dated 6 February 2004:

- ~ Revised the statistical methods to clarify the determination of statistical significance for the primary efficacy variable.
- ~ Clarified the expected response rate for allopurinol in the study and how this response rate was determined.
- ~ Incorporated 4 new references.
- ~ Updated TAP personnel job titles and added an additional TAP medical monitor.
- ~ Updated safety information in the introduction.

### **Statistical Methods Changes**

The following changes were made to the planned statistical analyses to provide a more complete set of analyses. In general, these changes were done after the blind was broken to clarify the results and to add additional exploratory analyses.

The data collection window was clarified to state that all laboratory and vital signs data collected within 1 day of the final dose would be used in the safety analyses. The definition of the 'final visit' was clarified to state that each subject's last post-baseline visit would be used in the analyses (ie, the baseline value would not be used as the 'final visit').

The timing of premature discontinuations was added to the summary of subject disposition for completeness. Separate summaries were generated for concomitant gout medications taken at any time and taken during a gout flare to further characterize concomitant gout medication usage. In analyses using overall compliance, compliances >100% were set to 100%. Treatment duration was summarized in weeks instead of days.

Additional analyses for the primary efficacy variable were conducted by adjusting for low-dose aspirin use, tobacco use, baseline calculated creatinine clearance (using the Cockcroft-Gault equation with ideal body weight), and metabolic syndrome to further investigate possible explanatory factors. Demographic summaries were also added for these factors as necessary. Calculation of creatinine clearance with the Cockcroft-Gault equation using ideal body weight was performed since high mean body weights were observed in this study population. The overall compliance subgroups were revised since few subjects had overall compliance <80%.

The analysis subset for the secondary efficacy variable of percent change in primary tophus size was redefined to use subjects with a primary palpable tophus at the Screening Visit instead of subjects with palpable tophi at the Screening Visit since a primary tophus could not be identified for some subjects with palpable tophi at the Screening Visit.

The number and percentage of subjects whose serum urate levels were <6.0 mg/dL at the Final Visit were summarized by treatment group and baseline serum urate level to further examine the effect of baseline serum urate level. The treatment groups were compared for the percent change

in primary tophus size and change in the total number of tophi per subject using Wilcoxon rank-sum tests instead of ANOVA based on a blinded review of the distribution of values. An analysis of subjects requiring treatment for a monoarticular or polyarticular gout flare was added to explore the treatment effect on flares in multiple joints. Additional pairwise comparisons were performed for the percentage of subjects requiring treatment for a gout flare at the last time period (Week 48 to 52). An additional analysis was conducted for the percent change in primary tophus size after excluding elbow tophi to evaluate the influence of elbow measurements on the overall results.

Additional summaries for the percent change in primary tophus size and percentage of subjects requiring treatment for a gout flare were conducted for subjects with an average post-baseline serum urate level <6.0 mg/dL or >6.0 mg/dL to examine the effect of serum urate reduction on these variables.

Additional safety analyses were conducted for subjects with potentially concerning vital signs and subjects with treatment-emergent ECG findings.

SAS for Unix was used instead of SAS for Windows in all analyses.

### 3. Post Hoc changes

None were noted.

### 4. Results

#### 4.1 Disposition

#### **Disposition of Subjects**

Seven hundred sixty subjects were randomized into the study in the US and Canada and received at least 1 dose of study drug (256 received febuxostat 80 mg QD, 251 received febuxostat 120 mg QD, and 253 received allopurinol 300 mg QD).

Overall, 33% (252/760) of the subjects prematurely discontinued treatment; 88 (34%) subjects discontinued from the febuxostat 80 mg QD group, 98 (39%) subjects discontinued from the febuxostat 120 mg QD group, and 66 (26%) subjects discontinued from the allopurinol 300 mg QD group. Of the subjects who prematurely discontinued from the study, 44% (111/252) discontinued within the first 12 weeks and discontinuation rates declined thereafter. A greater proportion of subjects in the febuxostat 120 mg QD treatment group prematurely discontinued within the first

12 weeks of the study (53%; 52/98) compared to the febuxostat 80 mg QD (41%; 36/88) and allopurinol 300 mg QD (35%; 23/66) treatment groups. The most frequent primary reason for discontinuing study drug overall was lost to follow-up (25%, 64 subjects) as documented by the investigator on the CRFs. A greater proportion of subjects in the febuxostat 120 mg QD treatment group prematurely discontinued treatment due to gout

flare and adverse events (29% and 23%, respectively) compared to the febuxostat 80 mg QD (11% and 18%, respectively) and allopurinol 300 mg QD (14% and 12%, respectively) treatment groups. Thirty-nine subjects discontinued from the study due to a primary reason of ‘other’; withdrawal of consent (9 subjects) and noncompliance (8 subjects) were the most frequently reported ‘other’ reasons for discontinuation.

**Table 56 : Timing and Reasons for Premature Discontinuation**

	Febuxostat 80 mg QD	Febuxostat 120 mg QD	Allopurinol 300 mg QD	All Subjects
All Randomized Subjects	256	251	253	760
	n (%)			
Completed Study	168 (66%)	153 (61%)	187 (74%)	508 (67%)
Prematurely Discontinued	88 (34%)	98 (39%)	66 (26%)	252 (33%)
Timing of Premature Discontinuations (weeks) <sup>a</sup>				
<4	15 (17%)	15 (15%)	12 (18%)	42 (17%)
4-<8	11 (13%)	20 (20%)	5 (8%)	36 (14%)
8-<12	10 (11%)	17 (17%)	6 (9%)	33 (13%)
12-<24	21 (24%)	25 (26%)	22 (33%)	68 (27%)
24-<36	17 (19%)	11 (11%)	12 (18%)	40 (16%)
36-<48	14 (16%)	10 (10%)	9 (14%)	33 (13%)
48-<52	0	0	0	0
Primary Reason <sup>a</sup> :				
Lost to follow-up	25 (28%)	18 (18%)	21 (32%)	64 (25%)
Adverse event	16 (18%)	23 (23%)	8 (12%)	47 (19%)
Gout flare	10 (11%)	28 (29%)	9 (14%)	47 (19%)
Personal reason(s)	19 (22%)	13 (13%)	13 (20%)	45 (18%)
Other	11 (13%)	14 (14%)	14 (21%)	39 (15%)
Protocol violation	7 (8%)	2 (2%)	1 (2%)	10 (4%)

a Denominator is the number of subjects who prematurely discontinued from each group.  
 Statistical Tables 14.1.1 and 14.1.2.1 and Appendix 16.2-1.1

*Reviewers comments: completion rate was highest in the allopurinol group, perhaps because of the greater incidence of gout flares in the febuxostat treatment groups. Because the primary efficacy variable relies on a responder analysis, dropouts will not need imputation. Therefore, the difference in dropout rates should not adversely affect our ability to analyze the trial. Dropouts due to “other” or “personal reasons” may be more problematic for safety analyses.*

### Protocol Deviations

A total of 50 subjects (16 febuxostat 80 mg QD, 15 febuxostat 120 mg QD and 19 allopurinol 300 mg QD) had deviations from the admission criteria for the study.

Four subjects (2 febuxostat 80 mg QD [2451 and 2786], 1 febuxostat 120 mg QD [2857], and 1 allopurinol 300 mg QD [2065]) were prematurely discontinued due to admission criteria violations at the request of TAP.

Most of the admission criteria violations were associated with subjects whose alcohol intake was  $\geq 14$  drinks/week (7 febuxostat 80 mg QD, 4 febuxostat 120 mg QD, and 5 allopurinol 300 mg QD). Of the departures approved by TAP, subjects were instructed by the site to drink less than 14 drinks/week during the study.

A total of 11 subjects had abnormal renal function (4 febuxostat 80 mg QD, 3 febuxostat 120 mg QD, and 4 allopurinol 300 mg QD). Subjects had their renal function assessed by a 24-hour creatinine clearance. Ten of the 11 subjects had either estimated or measured creatinine clearances  $>50$  mL/min or  $>50$  mL/min/1.73 m<sup>2</sup>, respectively, and were allowed to enter the study. One subject (2170) had a measured 24-hour creatinine clearance of 37 mL/min/1.73 m<sup>2</sup> (estimated creatinine clearance = 49 mL/min) and was discontinued from the study.

Eight subjects had serum urate levels  $<8.0$  mg/dL without concomitant uric acid-lowering therapy (1 febuxostat 80 mg QD, 3 febuxostat 120 mg QD, and 4 allopurinol 300 mg QD). All 8 subjects had serum urate levels  $>8.0$  mg/dL at the Day -2 Visit and were therefore eligible to be randomized. Two subjects (2215 and 2221) were on allopurinol prior to Day -14 (end Day -21 and Day -9, respectively) and needed additional time to sufficiently wash out their prior medication.

Four subjects (2076, 2147, 2413, and 2616) had a Day -2 serum urate level  $<8.0$  mg/dL based on central laboratory results (1 febuxostat 80 mg QD, 1 febuxostat 120 mg QD, and 2 allopurinol 300 mg QD). For 2 subjects (2076 and 2147), TAP did not receive notification of these departures until they had been randomized, although these subjects were allowed to continue. For the other 2 subjects (2413 and 2616), the serum urate level was  $<8.0$  mg/dL based on the Day -2 analysis window and was not considered as a protocol deviation at the time of enrollment. All 4 of these subjects' data were excluded from the efficacy analyses.

Five subjects (2128, 2132, 2222, 2658, and 2811) had concomitant thiazide diuretic therapy (2 febuxostat 80 mg QD and 3 febuxostat 120 mg QD). Three subjects (2128, 2132, and 2222) switched to Diovan (valsartan) or a loop diuretic prior to randomization. Subject 2811 continued in the study on Zaroxolyn, approved by the TAP Medical Monitor, after review of subject's medical history and the investigator's assurance that the subject was stable. Subject 2658 took Diovan HCT throughout study. TAP was notified after the subject was in the study for  $>7$  months; the subject completed the study without any drug-related adverse events.

Two subjects (2622 and 2623) had concomitant urate-lowering therapy (1 febuxostat 120 mg QD [allopurinol] and 1 allopurinol 300 mg QD [ColBenemid]). These subjects underwent appropriate washout of the urate-lowering therapy prior to randomization. Three subjects (2652, 2786, and 2520) had active liver disease at the Screening Visit as defined by an ALT and AST  $>1.5$  times the upper limit of normal at baseline (2 febuxostat 80 mg QD and 1 allopurinol 300 mg QD). Subject 2652 took 1 dose of study drug before the subject's Day -2 liver function tests (LFTs) were reviewed and the

Clinical Review  
{Schiffenbauer, Joel}  
{NDA 21-856}  
{Uloric/febuxostat}

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subject was discontinued from the study. Subject 2520 was enrolled in the study with exclusionary LFTs; however, the subject's LFTs were reviewed at Week 28 by the TAP Medical Monitor (when TAP was notified) and upon review, the subject was allowed to continue with frequent monitoring. The subject completed the study. Subject 2786 was randomized in error due to elevated LFTs and was discontinued from the study after 7 days of dosing.

Three subjects (2065, 2170, and 2857) reported a history of cancer within 5 years prior to enrollment in the study. Subject 2065 (allopurinol 300 mg QD) reported a history of cancer within 5 years and was discontinued from the study after 89 days of treatment. Subject 2170 (allopurinol 300 mg QD) had a history of squamous cancer within 5 years prior to randomization and was allowed to continue in the study since the subject was stable. Subject 2857 (febuxostat 120 mg QD) reported a history of cancer within 5 years and was discontinued from the study after 55 days of treatment.

One subject (Subject 2226) had 5 out of 6 preliminary criteria of the ARA for the classification of the acute arthritis of primary gout. The subject reported having gout flares in the past and had a serum urate level >8.0 mg/dL; however, the subject could not recall if the symptom of redness over joints was present during a flare.

One subject (Subject 2623) was taking aspirin 325 mg at the Screening Visit. The subject discontinued aspirin at Day -2 prior to randomization and was allowed to enroll in the study.

**Table 57 : Subjects with Admission Criteria Deviations**

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Clinical Review  
 {Schiffenbauer, Joel}  
 {NDA 21-856}  
 {Uloric/febuxostat}

Protocol Deviation	Febuxostat 80 mg QD	Febuxostat 120 mg QD	Allopurinol 300 mg QD
<b>Inclusion Criteria</b>			
History or presence of gout defined as having 1 or more of the ACR Preliminary criteria for diagnosis of gout			2226 <sup>a</sup>
Normal renal function	2132, 2294 <sup>a</sup> , 2466 <sup>a</sup> , 2487 <sup>a</sup>	2277 <sup>a</sup> , 2322 <sup>a</sup> , 2483 <sup>a</sup>	2170, 2186, 2210 <sup>a</sup> , 2384 <sup>a</sup>
Hyperuricemia (serum urate level $\geq$ 8.0 mg/dL on Day -2)	2076 <sup>a</sup>	2413 <sup>b</sup>	2147 <sup>a</sup> , 2616 <sup>b</sup>
<b>Exclusion Criteria</b>			
Concomitant therapy with any systemic or topical medications containing aspirin or other salicylates at the Screening Visit			2623
Thiazide diuretic therapy	2128, 2132 <sup>a</sup>	2222 <sup>a</sup> , 2658 <sup>a</sup> , 2811 <sup>a</sup>	
Alcohol intake $\geq$ 14 drinks/week	2008, 2220, 2314, 2451, 2624, 2727, 2789 <sup>a</sup>	2039 <sup>a</sup> , 2081, 2171, 2364	2127, 2268, 2449 <sup>a</sup> , 2465, 2877
Concomitant urate-lowering therapy		2622	2623
Active liver disease or hepatic dysfunction	2652, 2786		2520 <sup>a</sup>
Serum urate level $<$ 8.0 mg/dL and not taking uric acid-lowering therapy	2059 <sup>a</sup>	2060 <sup>a</sup> , 2100 <sup>a</sup> , 2364 <sup>a</sup>	2215 <sup>a</sup> , 2221 <sup>a</sup> , 2698, 2850 <sup>a</sup>
History of cancer		2857	2065, 2170

a Protocol departure approved by sponsor

b Protocol departure based on Day -2 analysis window and not considered a deviation at time of enrollment

Appendix 16.2-2.2

**Table 58 : Summary of Concomitant Medication Deviations**

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ON ORIGINAL

	Treatment Group n (%)		
	Febuxostat 80 mg QD (N=256)	Febuxostat 120 mg QD (N=251)	Allopurinol 300 mg QD (N=253)
<b>Prohibited Medications</b>			
Allopurinol	1 (<1%)	3 (1%)	3 (1%)
Chronic (>100 consecutive days) NSAIDs use	22 (9%)	31 (12%)	16 (6%)
Losartan potassium	3 (1%)	3 (1%)	0
Salicylate-containing medications (other than low-dose aspirin)	7 (3%)	2 (1%)	9 (4%)
Thiazide diuretics	2 (1%)	5 (2%)	4 (2%)
Trimethoprim-sulfamethoxazole	3 (1%)	2 (1%)	5 (2%)
Uricosurics and Sulfipyrazone	1 (<1%)	0	1 (<1%)
<b>Allowed Medications Above, Low Stable Doses</b>			
Ascorbic acid (>500 mg/day)	7 (3%)	4 (2%)	6 (2%)
Aspirin (>325 mg/day)	6 (2%)	8 (3%)	2 (1%)
Nicotinic acid (>500 mg/day)	2 (1%)	4 (2%)	2 (1%)
Prednisone (>10 mg/day)	49 (19%)	62 (25%)	39 (15%)

Appendices 16.2-7.5.1 and 16.2-7.5.2

Reviewers comments: relatively few subjects (compared to the total number of subjects) took a prohibited medication, and the numbers are fairly well balanced among groups.

#### 4.2 Demographics

#### Data Sets Analyzed

The primary and secondary efficacy analyses were based on the ITT population, which included all randomized subjects who received at least 1 dose of study drug and had a serum urate level of  $\geq 8.0$  mg/dL on Day -2 as determined by the central laboratory (Table XXX). Four randomized subjects (1 febuxostat 80 mg QD [2076], 1 febuxostat 120 mg QD [2413] and 2 allopurinol 300 mg QD [2147 and 2616]) were excluded from the ITT population since their Day -2 serum urate level was  $< 8.0$  mg/dL.

**Table 59** : Number of Subjects in Each Data Set

	Febuxostat 80 mg QD	Febuxostat 120 mg QD	Allopurinol 300 mg QD
All Randomized Subjects	256	251	253
ITT Subjects <sup>a</sup>	255	250	251

<sup>a</sup> Defined as randomized subjects who took at least 1 dose of study drug and had serum urate levels  $\geq 8.0$  mg/dL at Day -2 as determined by the central laboratory

Statistical Table 14.1.2.1

*Reviewer comments: only 4 subjects were excluded from the ITT analysis.*

### **Demographics**

No clinically relevant differences were observed across treatment groups in any demographic or baseline characteristic. Among all subjects, there were no statistically significant differences among the treatment groups in gender, race, age, weight, height, tobacco use, alcohol use, or BMI. Overall, subjects ranged in age from 23 to 83 years. The mean age ranged from 51.6 to 52.0 years among all treatment groups. In all of the treatment groups, the majority of the study population was Caucasian (75%) and most subjects were male (95%). The majority of subjects reported the use of alcohol (63%) and were non-/ex-tobacco users (82%). The mean BMI for all subjects was 32.5 kg/m<sup>2</sup> and 62% had a BMI of 30 kg/m<sup>2</sup>.

**Table 60** : Demographic Data at Baseline - All Subjects

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ON ORIGINAL

Variable	Febuxostat 80 mg QD (N=256)	Febuxostat 120 mg QD (N=251)	Allopurinol 300 mg QD (N=253)	All Subjects (N=760)
<b>Gender</b>				
Female	13 (5%)	8 (3%)	10 (4%)	31 (4%)
Male	243 (95%)	243 (97%)	243 (96%)	729 (96%)
<b>Race</b>				
Caucasian	193 (75%)	199 (79%)	195 (77%)	587 (77%)
Black	24 (9%)	20 (8%)	18 (7%)	62 (8%)
Hispanic	22 (9%)	17 (7%)	19 (8%)	58 (8%)
Asian	10 (4%)	9 (4%)	6 (2%)	25 (3%)
Other	7 (3%)	6 (2%)	15 (6%)	28 (4%)
<b>Age (years)<sup>a</sup></b>				
<45	75 (29%)	71 (28%)	84 (33%)	230 (30%)
45-<65	140 (55%)	133 (53%)	125 (49%)	398 (52%)
≥65	41 (16%)	47 (19%)	44 (17%)	132 (17%)
Mean (SD)	51.8 (11.69)	52.0 (12.12)	51.6 (12.63)	51.8 (12.13)
Range	25-81	23-81	24-83	23-83
<b>Weight (pounds)<sup>a</sup></b>				
Mean (SD)	224.7 (44.02)	223.9 (44.63)	224.8 (45.14)	224.5 (44.54)
Range	133-388	143-390	136-447	133-447
<b>Height (inches)<sup>a</sup></b>				
N	256	251	250	757
Mean (SD)	69.5 (3.19)	69.7 (3.09)	69.6 (3.15)	69.6 (3.14)
Range	60-80	59-79	59-78	59-80
<b>BMI (kg/m<sup>2</sup>)<sup>a</sup></b>				
N	256	251	250	757
<18.5	0	0	0	0
18.5-<25	15 (6%)	12 (5%)	7 (3%)	34 (4%)
25-<30	75 (29%)	87 (35%)	89 (35%)	251 (33%)
≥30	166 (65%)	152 (61%)	154 (61%)	472 (62%)
Missing	0	0	3 (1%)	3 (<1%)
Mean (SD)	32.7 (6.12)	32.3 (5.69)	32.6 (6.11)	32.5 (5.97)
Range	23-60	22-57	21-64	21-64
<b>Menopausal History (females)</b>				
N	13	8	10	31
Premenopausal	3 (23%)	0	0	3 (10%)
Perimenopausal	2 (15%)	0	0	2 (6%)
Postmenopausal	8 (62%)	8 (100%)	10 (100%)	26 (84%)
<b>Tobacco Use</b>				
Non-/Ex-Tobacco User	213 (83%)	208 (83%)	208 (82%)	629 (83%)
Tobacco User	43 (17%)	43 (17%)	45 (18%)	131 (17%)
<b>Alcohol Use</b>				
Non-/Ex-Drinker	85 (33%)	93 (37%)	80 (32%)	258 (34%)
Drinker	171 (67%)	158 (63%)	173 (68%)	502 (66%)

<sup>a</sup> At baseline

Statistical Table 14.1.3.1 and Appendices 16.2-4.1, 16.2-4.3, and 16.2-4.5

### 4.3 Baseline characteristics

**Table 61 : Baseline Medical Conditions - All Subjects**

Medical Condition	Febuxostat 80 mg QD (N=256)	Febuxostat 120 mg QD (N=251)	Allopurinol 300 mg QD (N=253)	All Subjects (N=760)
Impaired Renal Function <sup>a</sup>	3 (1%)	4 (2%)	4 (2%)	11 (1%)
Congestive Heart Failure	4 (2%)	3 (1%)	3 (1%)	10 (1%)
Cardiovascular Disease	23 (9%)	28 (11%)	23 (9%)	74 (10%)
Diabetes	17 (7%)	17 (7%)	19 (8%)	53 (7%)
Hypercholesterolemia	19 (7%)	25 (10%)	27 (11%)	71 (9%)
Hyperlipidemia	90 (35%)	79 (31%)	86 (34%)	255 (34%)
Hypertension	106 (41%)	113 (45%)	112 (44%)	331 (44%)
Obesity <sup>b</sup>	166 (65%)	152 (61%)	154 (61%)	472 (62%)
Use of Low-Dose Aspirin <sup>c</sup>	41 (16%)	51 (20%)	36 (14%)	128 (17%)
Metabolic Syndrome <sup>d</sup>	19 (7%)	25 (10%)	19 (8%)	63 (8%)
Calculated Creatinine Clearance (mL/min) <sup>e</sup>				
<50	13 (5%)	8 (3%)	13 (5%)	34 (4%)
50-<80	77 (30%)	90 (36%)	68 (27%)	235 (31%)
80-<120	138 (54%)	130 (52%)	140 (55%)	408 (54%)
≥120	28 (11%)	23 (9%)	29 (11%)	80 (11%)
Missing	0	0	3 (1%)	3 (<1%)
Mean (SD)	89.7 (24.44)	89.0 (27.74)	91.4 (26.47)	90.0 (26.22)
Range	31-167	39-252	26-170	26-252

- a Defined as serum creatinine >1.5 mg/dL or calculated creatinine clearance <50 mL/minute with calculated creatinine clearance based on the Cockcroft-Gault equation using actual body weight per Inclusion Criteria 4
- b Body mass index ≥30 kg/m<sup>2</sup>
- c Defined as a total dose ≤325 mg/day that was ongoing at the time of study completion
- d Defined as subjects who met all of the following criteria at baseline: triglycerides ≥150 mg/dL, systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥85 mm Hg, and fasting glucose ≥110 mg/dL
- e Calculated creatinine clearance based on the Cockcroft-Gault equation using ideal body weight. Statistical Table 14.1.3.1 and Appendices 16.2-4.1, 16.2-4.2, 16.2-7.5.1, 16.2-8.4.1, 16.2-8.4.2, 16.2-8.4.4, 16.2-8.5.1, and 16.2-8.9.1

**Table 62 : Gout Disease History - All Subjects**

Variable	Febuxostat 80 mg QD (N=256)	Febuxostat 120 mg QD (N=251)	Allopurinol 300 mg QD (N=253)	All Subjects (N=760)
<b>Years with Gout</b>				
Mean (SD)	11.5 (9.45)	12.6 (9.94)	11.6 (9.28)	11.9 (9.56)
Range	<1-43	<1-43	<1-51	<1-51
<b>Years Since Last Gout Flare</b>				
>10	2 (1%)	1 (<1%)	2 (1%)	5 (1%)
6-10	3 (1%)	1 (<1%)	7 (3%)	11 (1%)
1-5	27 (11%)	24 (10%)	28 (11%)	79 (10%)
<1	223 (87%)	225 (90%)	216 (85%)	664 (87%)
Missing	1 (<1%)	0	0	1 (<1%)
<b>Previous Use of Urate-Lowering Therapy</b>				
Prior Use	112 (44%)	106 (42%)	113 (45%)	331 (44%)
No Prior Use	144 (56%)	145 (58%)	140 (55%)	429 (56%)
<b>History of Renal Calculi</b>				
Yes	49 (19%)	34 (14%)	40 (16%)	123 (16%)
No	207 (81%)	217 (86%)	213 (84%)	637 (84%)
<b>History or Presence of a Tophus</b>				
Yes	59 (23%)	65 (26%)	62 (25%)	186 (24%)
No	197 (77%)	186 (74%)	191 (75%)	574 (76%)
<b>Years Since First Tophus Onset<sup>a</sup></b>				
N	59	65	59	183
Mean (SD)	6.0 (6.79)	7.4 (7.95)	7.5 (7.24)	7.0 (7.36)
Range	<1-33	<1-36	<1-31	<1-36
<b>Presence of a 1° Palpable Tophus</b>				
Yes	52 (20%)	53 (21%)	46 (18%)	151 (20%)
No but other tophi present	1 (<1%)	2 (1%)	3 (1%)	6 (1%)
No and no other tophi present	203 (79%)	196 (78%)	204 (81%)	603 (79%)
<b>Total # of Palpable Tophi Present<sup>b</sup></b>				
N	53	55	49	157
Mean (SD)	2.1 (1.58)	3.1 (3.61)	4.1 (6.35)	3.1 (4.29)
Range	1-7	1-19	1-38	1-38
<b>Site of 1° Palpable Tophus<sup>c</sup></b>				
N	52	53	46	151
Wrist/hand	7 (13%)	7 (13%)	4 (9%)	18 (12%)
Ankle/foot/toe/instep	18 (35%)	17 (32%)	8 (17%)	43 (28%)
Elbow	21 (40%)	21 (40%)	23 (50%)	65 (43%)
Knee	2 (4%)	4 (8%)	7 (15%)	13 (9%)
Other	4 (8%)	4 (8%)	4 (9%)	12 (8%)
<b>Size of 1° Palpable Tophus (mm)<sup>d</sup></b>				
N	52	53	46	151
Mean (SD)	1530.7 (2003.45)	1686.1 (2227.01)	1724.1 (2376.79)	1644.2 (2187.65)
Range	5-8100	8-11875	42-12954	5-12954

a Included only subjects with a history or presence of a tophus at baseline

b Included only subjects who had a palpable tophus identified at baseline

c Included only subjects who had a primary palpable tophus identified at baseline

Statistical Table 14.1.4.1 and Appendices 16.2-4.2, 16.2-4.4.1, 16.2-4.4.2, 16.2-4.4.3, 16.2-6.3.1, 16.2-6.3.2, and 16.2-7.5.2

*Reviewers comments: with minor variations, groups appear to be reasonably well balanced for a number of variables including years with gout, renal calculi, previous therapy etc.*

**Table 63 :** Baseline Serum Urate Level - ITT Subjects

Baseline Serum Urate (mg/dL)	Febuxostat 80 mg QD (N=255)	Febuxostat 120 mg QD (N=250)	Allopurinol 300 mg QD (N=251)	All ITT Subjects (N=756)
<9.0	75 (29%)	69 (28%)	63 (25%)	207 (27%)
9.0-<10.0	75 (29%)	81 (32%)	80 (32%)	236 (31%)
10.0-<11.0	68 (27%)	55 (22%)	58 (23%)	181 (24%)
11.0-<12.0	23 (9%)	32 (13%)	32 (13%)	87 (12%)
≥12.0	14 (5%)	13 (5%)	18 (7%)	45 (6%)
Mean (SD)	9.80 (1.245)	9.84 (1.265)	9.90 (1.231)	9.84 (1.246)
Range	7.7-14.5	7.4-14.9	7.3-13.5	7.3-14.9

Note: Baseline defined as the average of the Day -2 and Day 1 serum urate measurements  
 Statistical Table 14.1.5 and Appendix 16.2-6.1

*Reviewers comments: baseline serum urate levels are similar among the treatment groups.*

**Table 64 : All Concomitant Gout Medications Taken During a Gout Flare by Therapeutic Subclassification - All Subjects**

**APPEARS THIS WAY  
 ON ORIGINAL**

Clinical Review  
 {Schiffenbauer, Joel}  
 {NDA 21-856}  
 {Uloric/febuxostat}

Therapeutic Subclassification Medication	Treatment Group n (%)		
	Febuxostat 80 mg QD (N=256)	Febuxostat 120 mg QD (N=251)	Allopurinol 300 mg QD (N=253)
Total Subjects with at least 1 Concomitant Medication	152 (59%)	169 (67%)	159 (63%)
<b>Antibacterials for Systemic Use</b>	0	0	1 (<1%)
Cefalexin	0	0	1 (<1%)
<b>Antigout Preparations</b>	72 (28%)	71 (28%)	58 (23%)
Allopurinol	1 (<1%)	1 (<1%)	2 (<1%)
Colchicine	71 (28%)	70 (28%)	57 (23%)
Probenecid	1 (<1%)	0	0
<b>Anti-Inflammatory &amp; Antirheumatic Products</b>	116 (45%)	127 (51%)	128 (51%)
Arthrotec	1 (<1%)	2 (<1%)	1 (<1%)
Celecoxib	1 (<1%)	1 (<1%)	1 (<1%)
Diclofenac Sodium	1 (<1%)	1 (<1%)	0
Etodolac	0	1 (<1%)	0
Ibuprofen	19 (7%)	14 (6%)	18 (7%)
Indomethacin	51 (20%)	64 (25%)	65 (26%)
Ketoprofen	0	2 (<1%)	0
Ketorolac Tromethamine	2 (<1%)	6 (2%)	2 (<1%)
Meloxicam	3 (1%)	1 (<1%)	1 (<1%)
Naproxen	39 (15%)	41 (16%)	39 (15%)
Naproxen Sodium	8 (3%)	9 (4%)	11 (4%)
Rofecoxib	15 (6%)	10 (4%)	12 (5%)
Sulindac	0	1 (<1%)	0
Valdecoxib	2 (<1%)	0	5 (2%)

a Recorded as gout medication by the investigator  
 Statistical Table 14.1.6.3 and Appendix 16.2-7.5.2

APPEARS THIS WAY  
 ON ORIGINAL

Therapeutic Subclassification Medication	Treatment Group n (%)		
	Febuxostat 80 mg QD (N=256)	Febuxostat 120 mg QD (N=251)	Allopurinol 300 mg QD (N=253)
<b>Analgesics</b>	<b>20 (8%)</b>	<b>29 (12%)</b>	<b>20 (8%)</b>
Acetylsalicylic Acid	2 (<1%)	3 (1%)	0
Meperidine with Promethazine	1 (<1%)	0	0
Metamizole Sodium	0	1 (<1%)	0
Oxycocet	2 (<1%)	0	2 (<1%)
Oxycodone Acetaminophen	0	1 (<1%)	0
Panadeine CO	1 (<1%)	4 (2%)	1 (<1%)
Paracetamol	6 (2%)	6 (2%)	9 (4%)
Pethidine Hydrochloride	0	1 (<1%)	0
Propacet	0	3 (1%)	1 (<1%)
Thomapyrin N	1 (<1%)	0	0
Tramadol	0	0	1 (<1%)
Tramadol Hydrochloride	0	2 (<1%)	0
Ultracet	0	3 (1%)	1 (<1%)
Vicodin	11 (4%)	9 (4%)	9 (4%)
<b>Anesthetics</b>	<b>9 (4%)</b>	<b>4 (2%)</b>	<b>2 (&lt;1%)</b>
Bupivacaine	2 (<1%)	0	0
Lidocaine	5 (2%)	2 (<1%)	1 (<1%)
Lidocaine Hydrochloride	4 (2%)	2 (<1%)	0
Procaine	0	1 (<1%)	1 (<1%)
<b>Cough &amp; Cold Preparations</b>	<b>3 (1%)</b>	<b>1 (&lt;1%)</b>	<b>1 (&lt;1%)</b>
Hydrocodone	3 (1%)	1 (<1%)	1 (<1%)
<b>Corticosteroids for Systemic Use</b>	<b>39 (15%)</b>	<b>51 (20%)</b>	<b>29 (11%)</b>
Betamethasone Sodium Phosphate	1 (<1%)	0	0
Cortisone	1 (<1%)	0	0
Dexamethasone	2 (<1%)	1 (<1%)	1 (<1%)
Methylprednisolone	18 (7%)	27 (11%)	17 (7%)
Methylprednisolone Acetate	9 (4%)	13 (5%)	5 (2%)
Methylprednisolone Sodium Succinate	1 (<1%)	0	0
Prednisone	18 (7%)	18 (7%)	9 (4%)
Triamcinolone	0	1 (<1%)	0
Triamcinolone Acetonide	2 (<1%)	3 (1%)	1 (<1%)

a Recorded as gout medication by the investigator  
 Statistical Table 14.1.6.3 and Appendix 16.2-7.5.2

**Table 65 : Compliance**

Compliance	Febuxostat 80 mg QD (N=255)	Febuxostat 120 mg QD (N=250)	Allopurinol 300 mg QD (N=251)
<80%	7 (3%)	11 (4%)	7 (3%)
80-<90%	36 (14%)	29 (12%)	24 (10%)
≥90%	212 (83%)	210 (84%)	220 (88%)
Mean (SD)	95.1 (6.54)	95.0 (6.83)	95.5 (6.24)
Range	46-100	56-100	63-100

Statistical Table 14.1.8.2 and Appendices 16.2-5.2.1, 16.2-5.2.2, and 16.2-5.2.3

*Reviewers comments: compliance is comparable among the groups.*

#### 4.4 Efficacy

##### Primary

**Table 66 : Proportion of Subjects Whose Last 3 Serum Urate Levels were <6.0 mg/dL - ITT Subjects**

Last 3 Serum Urate Levels <6.0 mg/dL	Febuxostat 80 mg QD		Febuxostat 120 mg QD		Allopurinol 300 mg QD	
	n/N	(%)	n/N	(%)	n/N	(%)
Yes	136/255	(53%)	154/250	(62%)	53/251	(21%)
No	119/255	(47%)	96/250	(38%)	198/251	(79%)
	<b>Difference in Proportions</b>		<b>97.5% CI<sup>a</sup></b>		<b>P-value<sup>b</sup></b>	
Febuxostat 80 mg vs. Allopurinol	32%		(23.1%, 41.3%)		<0.001 <sup>c</sup>	
Febuxostat 120 mg vs. Allopurinol	41%		(31.5%, 49.5%)		<0.001 <sup>c</sup>	

a 97.5% confidence interval for the difference in proportions based on the normal approximation for the binomial distribution

b P-values from the Fisher's exact test

& Statistical significance versus allopurinol 300 mg QD at the 0.05 level based on Hochberg's procedure for multiple comparisons

Statistical Table 14.2.1.1

*Reviewers comments: As in trial 009, the primary analysis is a responder analysis of the subjects with the last 3 serum urate levels less than 6 (subjects could drop out early and be considered a responder as long as they had the last 3 urate levels less than 6; a completer analysis is shown below). Compared to allopurinol, febuxostat clearly shows evidence of efficacy.*

**Table 67 : Proportion of Subjects Whose Last 3 Serum Urate Levels were <6.0 mg/dL at Week 28 - ITT Subjects**

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Last 3 Serum Urate Levels <6.0 mg/dL	Febuxostat 80 mg QD		Febuxostat 120 mg QD		Allopurinol 300 mg QD	
	n/N	(%)	n/N	(%)	n/N	(%)
Yes	132/255	(52%) <sup>†</sup>	163/250	(65%)	50/251	(20%)
No	123/255	(48%)	87/250	(35%)	201/251	(80%)
	Difference in Proportions		97.5% CI <sup>a</sup>		P-value <sup>b</sup>	
Febuxostat 80 mg vs. Allopurinol	32%		(22.8%, 40.9%)		<0.001 <sup>c</sup>	
Febuxostat 120 mg vs. Allopurinol	45%		(36.5%, 54.1%)		<0.001 <sup>c</sup>	

- a 97.5% confidence interval for the difference in proportions based on the normal approximation for the binomial distribution  
 b P-values from the Fisher's exact test  
 & Statistical significance versus allopurinol 300 mg QD at the 0.05 level based on Hochberg's procedure for multiple comparisons  
 † Statistically significant difference versus febuxostat 120 mg QD (p≤0.05) using Fisher's exact test  
 Statistical Table 14.2.1.2

**Table 68: Proportion of Subjects Whose Last 3 Serum Urate Levels were <6.0 mg/dL by Baseline Serum Urate Level - ITT Subjects**

Baseline Serum Urate Level	Febuxostat 80 mg QD <sup>a</sup>		Febuxostat 120 mg QD <sup>a</sup>		Allopurinol 300 mg QD	
	n/N	(%)	n/N	(%)	n/N	(%)
<9.0 mg/dL	43/75	(57%)	50/69	(72%)	25/63	(40%)
9.0-<10.0 mg/dL	44/75	(59%)	60/81	(74%)	19/80	(24%)
≥10.0 mg/dL	49/105	(47%)	44/100	(44%)	9/108	(8%)

- a Statistically significant difference versus allopurinol 300 mg QD (p≤0.05) using a CMH test adjusting for the baseline serum urate level  
 Statistical Table 14.2.1.4

*Reviewers comments: Even when analyzed by baseline serum urate, febuxostat is superior to allopurinol, especially at urate levels higher than 10 mg/dL, where the allopurinol response rate drops off dramatically.*

Additional sensitivity analyses were requested from the sponsor and are provided below:

**Table 69: serum urate levels less than 6-completers**

Clinical Review  
 {Schiffenbauer, Joel}  
 {NDA 21-856}  
 {Uloric/febuxostat}

Proportion of Subjects with Last Three Serum Urate Levels  $\leq$  6.0 mg/dL - ITT Subjects  
 Subjects who Completed the Study

	Febuxostat 80 mg QD	Febuxostat 120 mg QD	Allopurinol 300 mg QD
Last 3 Serum Urate $\leq$ 6.0 mg/dL			
Yes	52.9% (185/187)	72.5% (111/153)	26.5% (49/185)
No	47.1% (43/187)	27.5% (42/153)	73.5% (136/185)
	Difference in Proportions	27.5% CI (a)	P-value (b)
Primary Comparisons			
Febux 80 mg vs Allop 300 mg	16.4%	( 35.3%, 27.5%)	<0.001*
Febux 120 mg vs Allop 300 mg	44.1%	( 35.2%, 56.5%)	<0.001*
Additional Comparisons			
Febux 80 mg vs Febux 120 mg			0.003*

(a) 95% confidence interval for the difference in proportions based on the normal approximation for the binomial distribution.  
 (b) P-values are from Fisher's Exact Test.  
 \* Indicates statistical significance at the 0.05 level based on Hochberg's procedure for multiple comparisons.

Reviewers comments: this is the completer analysis which confirms the primary analysis shown above.

Table 70: average serum urate levels less than 6

Proportion of Subjects with Average Serum Urate Levels  $\leq$  6.0 mg/dL - ITT Subjects

	Febuxostat 80 mg QD	Febuxostat 120 mg QD	Allopurinol 300 mg QD
Average Serum Urate $\leq$ 6.0 mg/dL			
Yes	75.3% (187/249)	87.6% (212/242)	39.3% (95/242)
No	24.7% (60/249)	12.4% (30/242)	60.7% (147/242)
	Difference in Proportions	27.5% CI (a)	P-value (b)
Primary Comparisons			
Febux 80 mg vs Allop 300 mg	16.4%	( 27.4%, 45.9%)	<0.001*
Febux 120 mg vs Allop 300 mg	46.3%	( 38.9%, 56.2%)	<0.001*
Additional Comparisons			
Febux 80 mg vs Febux 120 mg			0.001**

(a) 95% confidence interval for the difference in proportions based on the normal approximation for the binomial distribution.  
 (b) P-values are from Fisher's Exact Test.  
 \* Indicates statistical significance at the 0.05 level based on Hochberg's procedure for multiple comparisons.  
 \*\*, \*\*\* indicates statistical significance at the 0.05, 0.01, or 0.001 level, respectively.

Reviewers comments: this analysis of average serum urate less than 6 confirms the efficacy of febuxostat.

Table 71: all serum urate levels less than 6 after week 4

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 ON ORIGINAL

Clinical Review  
 {Schiffenbauer, Joel}  
 {NDA 21-856}  
 {Uloric/febuxostat}

Proportion of Subjects with All Serum Urate Levels < 6.0 mg/dL after Week 4 - ITT Subjects

	Febuxostat 80 mg QD	Febuxostat 120 mg QD	Allopurinol 300 mg QD
All Serum Urate < 6.0 mg/dL			
Yes	40.7% ( 87/213)	58.6% (150/256)	11.7% ( 27/231)
No	59.3% (126/213)	41.4% ( 92/222)	88.3% (204/231)
	Difference in Proportions	97.5% CI (a)	P-value (b)
Primary Comparisons			
Febux 80 mg vs Allo 300 mg	21.0%	( 20.1%, 21.9%)	<0.001*
Febux 120 mg vs Allo 300 mg	46.9%	( 38.1%, 55.7%)	<0.001*
Additional Comparisons			
Febux 80 mg vs Febux 120 mg			<0.001**

Success subjects are defined as serum urate < 6.0 mg/dL for every visit after Week 4.  
 The denominator for each treatment group is the number of subjects with at least one visit after Week 4.  
 (a) 97.5% confidence interval for the difference in proportions based on the normal approximation for the binomial distribution.  
 (b) P-values are from Fisher's Exact Test.  
 \* Indicates statistical significance at the 0.05 level based on Hochberg's procedure for multiple comparisons.  
 \*\*, \*\*\* indicates statistical significance at the 0.05, 0.01, or 0.001 level, respectively.

Reviewers comments: A drug that can lower serum urate and keep it consistently lower than 6 mg/dL is likely to be very efficacious. Febuxostat appears superior to allopurinol using this extremely high bar.

Table 72: all serum urate levels less than 6 -completers

Proportion of Subjects with All Serum Urate Levels < 6.0 mg/dL after Week 4 - ITT Subjects  
 Subjects who completed the study

	Febuxostat 80 mg QD	Febuxostat 120 mg QD	Allopurinol 300 mg QD
All Serum Urate < 6.0 mg/dL			
Yes	40.7% ( 68/167)	58.7% ( 69/118)	11.9% ( 21/176)
No	59.3% ( 99/167)	41.3% ( 49/118)	88.1% (155/176)
	Difference in Proportions	97.5% CI (a)	P-value (b)
Primary Comparisons			
Febux 80 mg vs Allo 300 mg	28.8%	( 19.9%, 37.7%)	<0.001*
Febux 120 mg vs Allo 300 mg	44.3%	( 31.8%, 56.8%)	<0.001*
Additional Comparisons			
Febux 80 mg vs Febux 120 mg			0.007**

Success subjects are defined as serum urate < 6.0 mg/dL for every visit after Week 4.  
 The denominator for each treatment group is the number of subjects who completed the study.  
 (a) 97.5% confidence interval for the difference in proportions based on the normal approximation for the binomial distribution.  
 (b) P-values are from Fisher's Exact Test.  
 \* Indicates statistical significance at the 0.05 level based on Hochberg's procedure for multiple comparisons.  
 \*\*, \*\*\* indicates statistical significance at the 0.05, 0.01, or 0.001 level, respectively.

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 ON ORIGINAL

*Reviewers comments: this is the completer analysis of the previous table and the results are consistent.*

**Secondary**

Multiple additional secondary analyses appear to demonstrate febuxostat's superiority to allopurinol.

**Table 73 : Proportion of Subjects with Serum Urate Levels <6.0 mg/dL, <5.0 mg/dL, and <4.0 mg/dL at the Week 28, Week 52, and Final Visits - ITT Subjects**

Visit	Febuxostat 80 mg QD		Febuxostat 120 mg QD		Allopurinol 300 mg QD	
	n/N	(%)	n/N	(%)	n/N	(%)
<b>&lt;6.0 mg/dL</b>						
Week 28	133/186	(72%) <sup>††</sup>	130/159	(82%) <sup>††</sup>	84/199	(42%)
Week 52	129/159	(81%) <sup>††</sup>	119/145	(82%) <sup>††</sup>	70/178	(39%)
Final	185/249	(74%) <sup>††</sup>	193/242	(80%) <sup>††</sup>	88/242	(36%)
<b>&lt;5.0 mg/dL</b>						
Week 28	93/186	(50%) <sup>††</sup>	108/159	(68%) <sup>††</sup>	20/199	(10%)
Week 52	87/159	(55%) <sup>††</sup>	103/145	(71%) <sup>††</sup>	26/178	(15%)
Final	118/249	(47%) <sup>††</sup>	160/242	(66%) <sup>††</sup>	31/242	(13%)
<b>&lt;4.0 mg/dL</b>						
Week 28	39/186	(21%) <sup>††</sup>	71/159	(45%) <sup>††</sup>	2/199	(1%)
Week 52	36/159	(23%) <sup>††</sup>	65/145	(45%) <sup>††</sup>	3/178	(2%)
Final	50/249	(20%) <sup>††</sup>	100/242	(41%) <sup>††</sup>	4/242	(2%)

a Statistically significant difference versus allopurinol 300 mg QD ( $p \leq 0.05$ ) using Fisher's exact test

† Statistically significant difference versus febuxostat 120 mg QD ( $p \leq 0.05$ ) using Fisher's exact test  
 Statistical Tables 14.2.2.1, 14.2.2.3, and 14.2.2.4

*Reviewers comments: again, febuxostat appears superior to allopurinol based on the ability to lower serum urate to even less than 4 mg/dL.*

**Table 74 : Proportion of Subjects with Serum Urate Level <6.0 mg/dL at the Final Visit by Baseline Serum Urate Level - ITT Subjects**

Baseline Serum Urate Level	Febuxostat 80 mg QD		Febuxostat 120 mg QD		Allopurinol 300 mg QD	
	n/N	(%)	n/N	(%)	n/N	(%)
<9.0 mg/dL	58/71	(82%) <sup>a</sup>	58/67	(87%) <sup>a</sup>	35/61	(57%)
9.0-<10.0 mg/dL	57/74	(77%) <sup>a,†</sup>	73/79	(92%) <sup>a</sup>	31/78	(40%)
≥10.0 mg/dL	70/104	(67%) <sup>a</sup>	62/96	(65%) <sup>a</sup>	22/103	(21%)

a Statistically significant difference versus allopurinol 300 mg QD (p≤0.05) using Fisher's exact test  
 † Statistically significant difference versus febuxostat 120 mg QD (p≤0.05) using Fisher's exact test  
 Statistical Table 14.2.2.2

**Table 75 : Median and Mean Percent Change from Baseline in Primary Tophus Size at the Week 28, Week 52, and Final Visits – ITT Subjects with a Primary Palpable Tophus at Baseline**

Visit	Febuxostat 80 mg QD			Febuxostat 120 mg QD			Allopurinol 300 mg QD		
	N	Median (25 <sup>th</sup> p., 75 <sup>th</sup> p.)	Mean	N	Median (25 <sup>th</sup> p., 75 <sup>th</sup> p.)	Mean	N	Median (25 <sup>th</sup> p., 75 <sup>th</sup> p.)	Mean
<b>Actual Value (mm<sup>3</sup>)</b>									
Baseline	52	677.0 (196.0, 2117.0)	1530.7	53	780.0 (400.0, 1935.0)	1686.1	45	928.0 (440.0, 2310.0)	1761.5
Week 28	36	484.0 (95.0, 1460.0)	920.9	28	277.5 (162.0, 723.0)	705.0	33	625.0 (200.0, 1664.0)	1261.1
Week 52	32	186.0 (0.0, 935.0)	517.0	26	289.5 (64.0, 864.0)	527.3	30	272.5 (100.0, 1482.0)	991.0
Final	50	276.0 (0.0, 1120.0)	564.1	51	361.0 (100.0, 1225.0)	1189.6	44	470.0 (115.0, 1632.0)	1486.6
<b>Percent Change from Baseline (%)</b>									
Week 28	36	-29.5 <sup>†</sup> (-66.0, 4.1)	63.6	28	-49.5 <sup>a</sup> (-80.8, -34.9)	-52.6	33	-28.6 (-54.9, 0.0)	-16.4
Week 52	32	-83.4 (-100.0, -15.6)	936.0	26	-65.5 (-85.5, -38.9)	-56.3	30	-49.7 (-96.0, 0.0)	-26.7
Final	50	-51.7 (-100.0, -8.3)	588.6	51	-43.8 (-83.0, 0.0)	-36.7	44	-39.6 (-65.0, 1.5)	-21.5

Note: Baseline was defined as the last examination prior to the first dose of study drug.

25<sup>th</sup> p. = 25<sup>th</sup> percentile; 75<sup>th</sup> p. = 75<sup>th</sup> percentile

a Statistically significant difference in percent change values versus allopurinol 300 mg QD (p≤0.05) using Wilcoxon rank-sum test

† Statistically significant difference in percent change values versus febuxostat 120 mg QD (p≤0.05) using Wilcoxon rank-sum test

Statistical Table 14.2.2.6

*Reviewers comments: baseline tophus size was greatest in the allopurinol group and the percent changes was the least. The apparently anomalous finding of a large percent change (for example the 926 and 588 percent change is due to 2 individuals with small tophi at baseline who had small absolute changes in size but large percent changes leading to the large mean changes. The sponsor provided an analysis without these 2 patients and the percent change is much smaller- data not included here).*

**Table 76 : Median and Mean Percent Change from Baseline in Primary Tophus Size by Average Post-Baseline Serum Urate Level at the Week 28, Week 52, and Final Visits - ITT Subjects with a Primary Palpable Tophus at Baseline**

Visit	Serum Urate <6.0 mg/dL			Serum Urate ≥6.0 mg/dL		
	N	Median (25 <sup>th</sup> p., 75 <sup>th</sup> p.)	Mean	N	Median (25 <sup>th</sup> p., 75 <sup>th</sup> p.)	Mean
<b>Actual Value (mm<sup>3</sup>)</b>						
Baseline	89	729.0 (270.0, 1800.0)	1354.1	55	1050.0 (396.0, 2640.0)	2029.5
Week 28	61	432.0 (100.0, 825.0)	706.1	36	766.5 (208.0, 1788.0)	1428.7
Week 52	54	181.5 (0.0, 864.0)	498.1	34	448.0 (120.0, 1225.0)	973.1
Final	89	300.0 (1.0, 1120.0)	700.0	54	530.0 (130.0, 1482.0)	1441.8
<b>Percent Change from Baseline (%)</b>						
Week 28	61	-47.2 (-78.6, -9.1)	15.4	36	-24.2 (-40.4, 0.0)	-18.5
Week 52	54	-75.0 (-100.0, -31.8)	540.0	34	-49.7 (-81.9, -7.4)	-43.3
Final	89	-54.7 (-99.8, -8.3)	315.0	54	-27.4 (-58.6, 0.0)	-26.8

Note: Baseline was defined as the last examination prior to the first dose of study drug.  
 25<sup>th</sup> p. = 25<sup>th</sup> percentile; 75<sup>th</sup> p. = 75<sup>th</sup> percentile  
 Statistical Tables 14.2.2.8 and 14.2.2.9

*Reviewers comments: those with serum urate less than 6 had a greater decrease in tophus size than those with serum urate greater than 6, although baseline size was much greater in the serum urate greater than 6 group (2029 vs 1354).*

**Table 77: Median and Mean Percent Change from Baseline in Primary Tophus Size at the Week 28, Week 52, and Final Visits – ITT Subjects with a Primary Palpable Tophus at Baseline and an Average Post-Baseline Serum Urate Level <6.0 mg/dL**

Visit	Febuxostat 80 mg QD			Febuxostat 120 mg QD			Allopurinol 300 mg QD		
	N	Median (25 <sup>th</sup> p., 75 <sup>th</sup> p.)	Mean	N	Median (25 <sup>th</sup> p., 75 <sup>th</sup> p.)	Mean	N	Median (25 <sup>th</sup> p., 75 <sup>th</sup> p.)	Mean
<b>Actual Value (mm<sup>3</sup>)</b>									
Baseline	36	612.5 (145.0, 1812.5)	1400.1	42	765.0 (270.0, 1848.0)	1359.7	11	912.0 (572.0, 1600.0)	1182.0
Week 28	26	416.0 (15.0, 840.0)	678.5	25	255.0 (156.0, 625.0)	615.9	10	756.0 (270.0, 1664.0)	1003.5
Week 52	22	2.5 (0.0, 1120.0)	493.9	22	225.5 (48.0, 440.0)	391.7	10	348.0 (100.0, 1600.0)	741.5
Final	36	42.0 (0.0, 997.5)	520.7	42	350.0 (64.0, 875.0)	831.3	11	528.0 (100.0, 1600.0)	785.5
<b>Percent Change from Baseline (%)</b>									
Week 28	26	-39.3 (-84.8, -6.0)	81.5	25	-50.0 (-83.0, -36.1)	-53.2	10	-20.3 (-57.6, 60.0)	14.9
Week 52	22	-93.4 (-100.0, -30.0)	1381.4	22	-73.8 (-89.7, -38.9)	-57.8	10	-49.9 (-96.3, 125.0)	3.9
Final	36	-65.3 (-100.0, -15.2)	829.5	42	-53.0 (-84.9, 0.0)	-43.2	11	-50.5 (-96.3, 125.0)	-1.1

Note: Baseline was defined as the last examination prior to the first dose of study drug.  
 25<sup>th</sup> p. = 25<sup>th</sup> percentile; 75<sup>th</sup> p. = 75<sup>th</sup> percentile  
 Statistical Table 14.2.2.8

*Reviewers comments: few subjects had an average decrease in serum urate to less than 6 in the allopurinol group (N=11) so the validity of the analysis is questionable.*

**Table 78 : Median and Mean Percent Change from Baseline in Primary Tophus Size at the Week 28, Week 52, and Final Visits – ITT Subjects with a Primary Palpable Tophus at Baseline and an Average Post-Baseline Serum Urate Level ≤6.0 mg/dL**

Visit	Febuxostat 80 mg QD			Febuxostat 120 mg QD			Allopurinol 300 mg QD		
	N	Median (25 <sup>th</sup> p., 75 <sup>th</sup> p.)	Mean	N	Median (25 <sup>th</sup> p., 75 <sup>th</sup> p.)	Mean	N	Median (25 <sup>th</sup> p., 75 <sup>th</sup> p.)	Mean
<b>Actual Value (mm<sup>2</sup>)</b>									
Baseline	15	1350.0 (375.0, 2400.0)	1926.1	8	1112.0 (430.0, 4475.0)	2306.1	32	975.5 (418.0, 2535.0)	2008.8
Week 28	10	1460.0 (900.0, 1800.0)	1551.1	3	1400.0 (192.0, 2750.0)	1447.3	23	484.0 (130.0, 1776.0)	1373.1
Week 52	10	557.5 (120.0, 750.0)	567.9	4	1250.0 (546.0, 2000.0)	1273.0	20	272.5 (80.0, 1333.0)	1115.8
Final	14	562.5 (120.0, 1225.0)	675.5	8	1050.0 (384.0, 2000.0)	1735.0	32	428.0 (115.0, 1866.0)	1703.7
<b>Percent Change from Baseline (%)</b>									
Week 28	10	8.3 (0.0, 18.5)	17.0	3	-39.6 (-78.1, -26.2)	-47.9	23	-30.6 (-54.9, -2.2)	-30.0
Week 52	10	-54.0 (-88.4, 0.0)	-44.0	4	-45.5 (-61.1, -35.0)	-48.0	20	-49.7 (-85.5, -3.7)	-42.0
Final	14	-24.6 (-81.9, 12.0)	-30.7	8	-23.1 (-45.5, 25.7)	-7.6	32	-33.2 (-59.0, 0.0)	-30.0

Note: Baseline was defined as the last examination prior to the first dose of study drug.  
 25<sup>th</sup> p. = 25<sup>th</sup> percentile; 75<sup>th</sup> p. = 75<sup>th</sup> percentile  
 Statistical Table 14.2.2.9

**Table 79 : Subjects Requiring Treatment for a Gout Flare by Time Interval - ITT Subjects**

Time Interval	Febuxostat 80 mg QD		Febuxostat 120 mg QD		Allopurinol 300 mg QD	
	n/N	(%)	n/N	(%)	n/N	(%)
Screening	20/255	(8%)	28/250	(11%)	20/251	(8%)
Day 1 to Week 52	163/255	(64%)	179/250	(72%)	163/251	(65%)
Day 1 to Week 8	55/255	(22%) <sup>†</sup>	90/250	(36%) <sup>a</sup>	52/251	(21%)
Week 8 to Week 52	147/228	(64%)	150/215	(70%)	150/234	(64%)
Week 8 to Week 16	110/228	(48%)	115/215	(53%)	101/234	(43%)
Week 16 to Week 24	75/210	(36%)	69/191	(36%)	67/216	(31%)
Week 24 to Week 32	55/197	(28%)	49/174	(28%)	55/205	(27%)
Week 32 to Week 40	38/188	(20%)	28/164	(17%)	41/196	(21%)
Week 40 to Week 48	30/177	(17%)	24/161	(15%)	33/191	(17%)
Week 48 to Week 52	13/167	(8%)	9/153	(6%)	20/185	(11%)
During Prophylaxis <sup>&amp;</sup>	56/253	(22%) <sup>†</sup>	90/250	(36%) <sup>a</sup>	52/248	(21%)
After Prophylaxis <sup>&amp;</sup>	146/253	(58%)	151/250	(60%)	151/248	(61%)

Note: The numerator is the number of subjects requiring treatment for a gout flare in the time interval and treatment group being summarized. The denominator is the number of subjects exposed to at least 1 dose of that treatment in the time interval being summarized.

- a Statistically significant difference versus allopurinol 300 mg QD (p≤0.05) using Fisher's exact test
- † Statistically significant difference versus febuxostat 120 mg QD (p≤0.05) using Fisher's exact test
- & Based on each subject's actual prophylaxis period. The denominator is the number of subjects with at least 1 prophylactic dose

Statistical Table 14.2.2.11

*Reviewers comments: interestingly the number of flares in the week 48-52 time period was similar to the rate of flares at screening and so does not definitively demonstrate a reduction in flare rate. The total number of flares is somewhat higher in the febuxostat 120 mg group during weeks 1-8 possibly due to the greater urate lowering ability of febuxostat compared to allopurinol. During weeks 48-52 the rate of flares is marginally higher in the allopurinol group but does not robustly demonstrate a reduction in flare rates in the febuxostat group. It is important to also compare these results to those of trial 009 (which had a placebo group, although only 6 months in duration). In trial 009, at the last time period (weeks 24-28) there was little difference between the placebo group and treatment groups. In total, although it appears that the gouty flare rate is decreasing the evidence for this is not convincing.*

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**Table 80 : Subjects Requiring Treatment for a Gout Flare by Time Interval - ITT Subjects with an Average Post-Baseline Serum Urate Level <6.0 mg/dL**

Time Interval	Febuxostat 80 mg QD		Febuxostat 120 mg QD		Allopurinol 300 mg QD	
	n/N	(%)	n/N	(%)	n/N	(%)
Screening	15/189	(8%)	21/212	(10%)	6/95	(6%)
Day 1 to Week 52	124/189	(66%)	159/212	(75%)	52/95	(55%)
Day 1 to Week 8	39/189	(21%)	79/212	(37%)	11/95	(12%)
Week 8 to Week 52	114/176	(65%)	133/190	(70%)	49/90	(54%)
Week 8 to Week 16	87/176	(49%)	103/190	(54%)	32/90	(36%)
Week 16 to Week 24	61/163	(37%)	61/170	(36%)	22/86	(26%)
Week 24 to Week 32	42/154	(27%)	40/154	(26%)	16/83	(19%)
Week 32 to Week 40	25/148	(17%)	24/146	(16%)	14/81	(17%)
Week 40 to Week 48	22/138	(16%)	19/143	(13%)	10/81	(12%)
Week 48 to Week 52	9/131	(7%)	6/136	(4%)	5/79	(6%)
During Prophylaxis <sup>&amp;</sup>	39/188	(21%)	79/212	(37%)	12/94	(13%)
After Prophylaxis <sup>&amp;</sup>	113/188	(60%)	133/212	(63%)	49/94	(52%)

Note: The numerator is the number of subjects requiring treatment for a gout flare in the time interval and treatment group being summarized. The denominator is the number of subjects exposed to at least 1 dose of that treatment in the time interval being summarized.

& Based on each subject's actual prophylaxis period. The denominator is the number of subjects with at least 1 prophylactic dose

Statistical Table 14.2.2.12

**Table 81 : Subjects Requiring Treatment for a Gout Flare by Time Interval - ITT Subjects with an Average Post-Baseline Serum Urate Level >6.0 mg/dL**

Time Interval	Febuxostat 80 mg QD		Febuxostat 120 mg QD		Allopurinol 300 mg QD	
	n/N	(%)	n/N	(%)	n/N	(%)
Screening	5/60	(8%)	7/30	(23%)	13/147	(9%)
Day 1 to Week 52	38/60	(63%)	19/30	(63%)	109/147	(74%)
Day 1 to Week 8	15/60	(25%)	10/30	(33%)	39/147	(27%)
Week 8 to Week 52	33/52	(63%)	17/25	(68%)	101/144	(70%)
Week 8 to Week 16	23/52	(44%)	12/25	(48%)	69/144	(48%)
Week 16 to Week 24	14/47	(30%)	8/21	(38%)	45/130	(35%)
Week 24 to Week 32	13/43	(30%)	9/20	(45%)	39/122	(32%)
Week 32 to Week 40	13/40	(33%)	4/18	(22%)	27/115	(23%)
Week 40 to Week 48	8/39	(21%)	5/18	(28%)	23/110	(21%)
Week 48 to Week 52	4/36	(11%)	3/17	(18%)	15/106	(14%)
During Prophylaxis <sup>&amp;c</sup>	16/59	(27%)	10/30	(33%)	38/145	(26%)
After Prophylaxis <sup>&amp;c</sup>	33/59	(56%)	18/30	(60%)	101/145	(70%)

Note: The numerator is the number of subjects requiring treatment for a gout flare in the time interval and treatment group being summarized. The denominator is the number of subjects exposed to at least 1 dose of that treatment in the time interval being summarized.

& Based on each subject's actual prophylaxis period. The denominator is the number of subjects with at least 1 prophylactic dose

Statistical Table 14.2.2.13

Finally, the sponsor was requested to provide a K-M analysis for time to (first) gout flare. In addition, the sponsor provided a K-M analysis of time to last flare (as discussed under trial 009). Both analyses are provided below.

**Table 82 : Time to First Post-Prophylaxis Gout Flare Kaplan-Meier Point Estimates and Test for Equality**

Treatment group	Mean (days)		Median (days)			p-value
			95% CI			
	Mean	Std. Error	Median	Lower	Upper	
Febuxostat 80 mg QD	153.9	5.89	114	102	138	0.0554
Febuxostat 120 mg QD	168.0	8.74	99	84	117	
Allopurinol 300/100 mg QD	205.0	9.10	160	108	198	

CI = Confidence Interval

**Figure 6: Kaplan Meier**

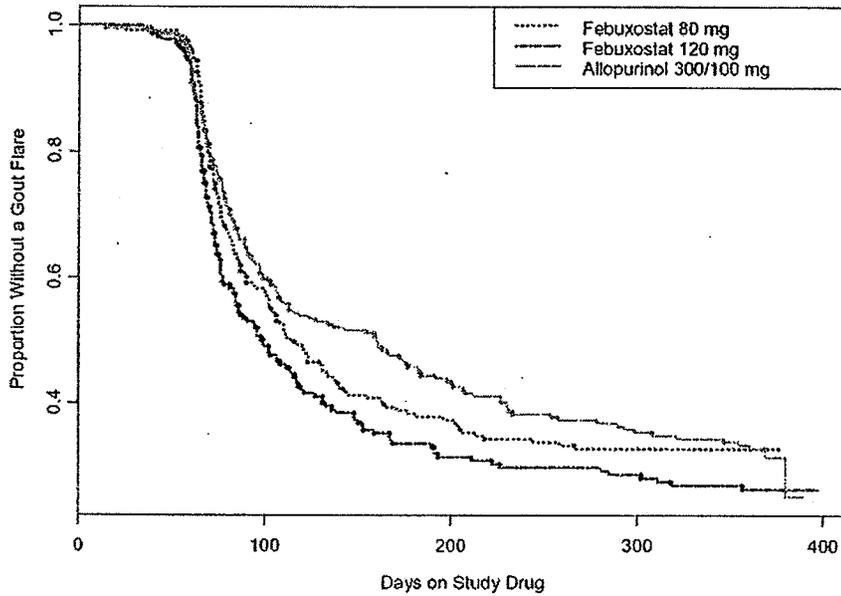
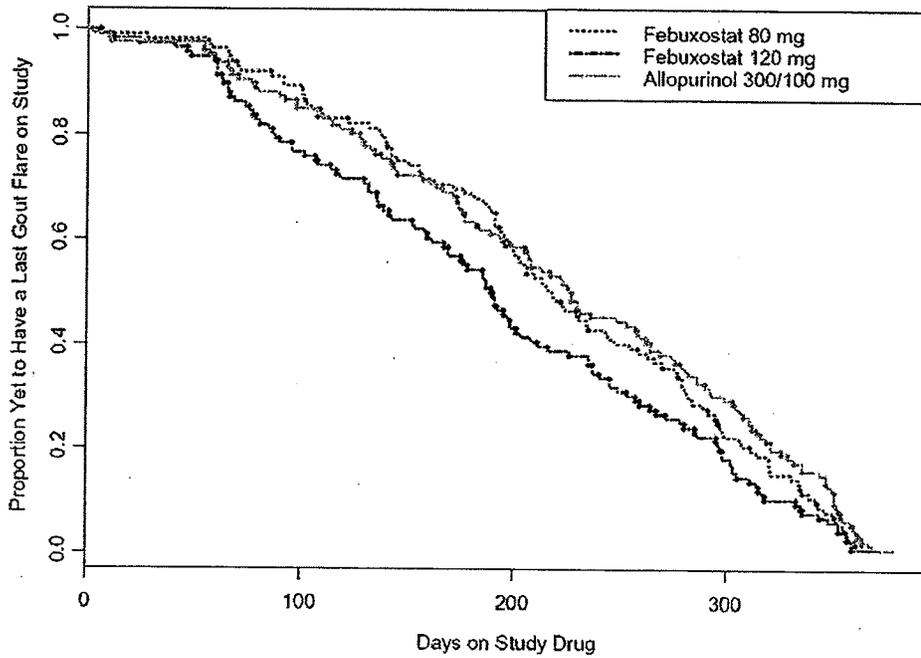


Table 83 : Time to Last Gout Flare Kaplan-Meier Point Estimates and Test for Equality

Treatment group	Mean (days)		Median (days)			p-value
	Mean	Std. Error	Median	95% CI		
				Lower	Upper	
Febuxostat 80 mg QD	219.6	8.66	217	196	247	0.0397
Febuxostat 120 mg QD	192.0	9.09	190	167	208	
Allopurinol 300/100 mg/QD	222.1	8.94	227	205	259	

Figure 7: Kaplan-Meier Function Estimates for Time to Last Gout Flare



*Reviewers comments: Trial 010 was a one year trial. The analysis of time to last flare suggests that the 120 mg dose has some efficacy in reducing flares but the K-M plots overlap at the final time point (numbers of subjects remaining at each time was not provided). Again, these are all post-hoc analyses and should not be considered as firm evidence of efficacy.*

**Table 84 : Mean Change from Baseline in SF-36™ Health Survey at the Week 24, Week 52, and Final Visits - ITT Subjects**

Area Domain Timepoint	Febuxostat 80 mg QD		Febuxostat 120 mg QD		Allopurinol 300 mg QD	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
<b>Functional Status</b>						
<b>Physical Functioning</b>						
Baseline	237	79.6 (22.01)	239	79.6 (22.14)	234	74.6 (25.13)
Δ at Week 24	170	3.2 <sup>‡</sup> (18.99)	158	0.5 (15.85)	176	2.0 (19.59)
Δ at Week 52	146	3.8 <sup>‡</sup> (18.86)	141	2.1 (20.08)	161	5.6 <sup>‡</sup> (20.58)
Δ at Final	212	1.2 <sup>a</sup> (23.46)	208	-1.4 <sup>a</sup> (24.08)	209	6.0 <sup>‡</sup> (21.21)
<b>Role-Physical</b>						
Baseline	237	71.4 (39.70)	238	70.1 (41.20)	234	67.8 (42.13)
Δ at Week 24	170	9.7 <sup>‡</sup> (46.09)	158	7.0 <sup>‡</sup> (41.27)	176	7.1 <sup>‡</sup> (42.75)
Δ at Week 52	144	11.6 <sup>‡</sup> (46.27)	141	14.5 <sup>‡</sup> (42.48)	161	14.6 <sup>‡</sup> (41.23)
Δ at Final	212	7.0 <sup>‡</sup> (46.96)	208	2.5 (49.05)	209	10.6 <sup>‡</sup> (40.99)
<b>Bodily Pain</b>						
Baseline	237	61.7 (25.39)	238	57.2 (25.16)	234	58.1 (27.21)
Δ at Week 24	170	6.8 <sup>‡</sup> (28.59)	158	7.6 <sup>‡</sup> (26.94)	176	6.6 <sup>‡</sup> (28.55)
Δ at Week 52	146	8.4 <sup>‡†</sup> (26.38)	141	14.8 <sup>‡</sup> (26.54)	161	13.1 <sup>‡</sup> (26.69)
Δ at Final	212	6.9 <sup>‡</sup> (28.85)	209	6.9 <sup>‡</sup> (30.01)	208	11.0 <sup>‡</sup> (28.45)
<b>General Health</b>						
Baseline	237	70.3 (17.90)	238	70.2 (19.25)	234	68.8 (19.16)
Δ at Week 24	169	0.2 (15.03)	157	-0.7 (12.76)	176	-0.7 (15.90)
Δ at Week 52	146	2.8 <sup>‡</sup> (13.37)	140	0.9 (14.21)	161	3.0 <sup>‡</sup> (15.62)
Δ at Final	212	1.7 (14.33)	208	-0.8 <sup>a</sup> (14.70)	208	2.2 (16.58)
<b>Vitality</b>						
Baseline	237	63.3 (18.78)	239	62.7 (18.42)	234	60.7 (20.46)
Δ at Week 24	170	1.1 (14.72)	158	0.7 (16.07)	176	0.4 (16.44)
Δ at Week 52	146	3.7 <sup>‡</sup> (16.18)	141	2.9 <sup>‡</sup> (14.26)	161	5.3 <sup>‡</sup> (16.54)
Δ at Final	212	1.8 (17.47)	209	0.1 <sup>a</sup> (17.19)	208	4.9 <sup>‡</sup> (17.47)

All scores are on a 0-100 scale with higher scores indicating better health.

Positive change from baseline indicates improvement.

‡ Statistically significant within group change from baseline (p≤0.05) using a paired t-test

a Statistically significant difference versus allopurinol 300 mg QD (p≤0.05) using ANOVA

† Statistically significant difference versus febuxostat 120 mg QD (p≤0.05) using ANOVA

Statistical Table 14.2.2.19

Area Domain Timepoint	Febuxostat 80 mg QD		Febuxostat 120 mg QD		Allopurinol 300 mg QD	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
<b>Functional Status</b>						
<b>Social Functioning</b>						
Baseline	237	82.5 (22.03)	239	84.3 (22.00)	234	80.7 (23.85)
Δ at Week 24	170	2.8 (21.06)	158	0.5 (21.30)	176	1.6 (23.53)
Δ at Week 52	146	3.9 <sup>‡</sup> (21.41)	141	2.4 <sup>a</sup> (18.95)	161	8.2 <sup>‡</sup> (20.12)
Δ at Final	212	2.4 <sup>‡</sup> (23.04)	209	-3.5 <sup>‡a</sup> (25.00)	209	6.7 <sup>‡</sup> (21.65)
<b>Role-Emotional</b>						
Baseline	237	88.0 (27.05)	238	86.3 (29.40)	234	82.5 (33.00)
Δ at Week 24	169	0.0 (32.53)	158	-0.8 (30.55)	176	3.4 (27.39)
Δ at Week 52	144	1.3 (32.27)	141	3.1 (29.79)	161	7.7 <sup>‡</sup> (29.87)
Δ at Final	212	-1.2 <sup>a</sup> (34.72)	208	-1.9 <sup>a</sup> (34.31)	209	5.3 <sup>‡</sup> (30.47)
<b>Mental Health</b>						
Baseline	237	80.2 (14.42)	239	79.9 (15.10)	234	79.5 (16.11)
Δ at Week 24	170	-0.7 (10.64)	158	-0.8 (14.16)	176	-0.7 (12.32)
Δ at Week 52	146	0.4 (13.63)	141	0.6 (12.31)	161	2.1 <sup>‡</sup> (10.87)
Δ at Final	212	0.0 (13.31)	209	-1.1 (14.95)	208	1.5 (13.41)
<b>Physical Component Summary</b>						
Baseline	237	46.8 (9.54)	236	46.2 (9.33)	234	45.2 (10.31)
Δ at Week 24	168	2.6 <sup>‡</sup> (9.63)	157	1.8 <sup>‡</sup> (7.83)	176	1.8 <sup>‡</sup> (9.31)
Δ at Week 52	144	3.2 <sup>‡</sup> (9.44)	140	3.7 <sup>‡</sup> (8.60)	161	3.9 <sup>‡</sup> (9.19)
Δ at Final	212	2.1 <sup>‡</sup> (9.94)	206	1.2 <sup>a</sup> (10.16)	207	3.4 <sup>‡</sup> (9.62)
<b>Mental Component Summary</b>						
Baseline	237	53.5 (7.97)	236	53.7 (7.89)	234	52.9 (9.58)
Δ at Week 24	168	-0.7 (7.46)	157	-0.8 (8.30)	176	-0.2 (7.36)
Δ at Week 52	144	-0.1 (8.75)	140	-0.1 (7.11)	161	1.6 <sup>‡</sup> (7.06)
Δ at Final	212	-0.4 (9.01)	206	-1.2 <sup>‡a</sup> (8.55)	207	1.1 (8.10)
<b>Reported Health Transition</b>						
Baseline	236	51.5 (16.88)	237	55.3 (19.76)	234	53.3 (17.86)
Δ at Week 24	168	9.8 <sup>‡</sup> (23.38)	155	6.3 <sup>‡</sup> (23.77)	175	8.3 <sup>‡</sup> (23.73)
Δ at Week 52	144	16.1 <sup>‡</sup> (24.46)	140	14.8 <sup>‡</sup> (23.21)	159	16.4 <sup>‡</sup> (27.84)
Δ at Final	211	12.6 <sup>‡</sup> (25.04)	206	8.1 <sup>‡a</sup> (26.20)	208	14.1 <sup>‡</sup> (27.54)

All scores are on a 0-100 scale with higher scores indicating better health.

Positive change from baseline indicates improvement.

‡ Statistically significant within group change from baseline (p≤0.05) using a paired t-test

a Statistically significant difference versus allopurinol 300 mg QD (p≤0.05) using ANOVA

† Statistically significant difference versus febuxostat 120 mg QD (p≤0.05) using ANOVA

Statistical Table 14.2.2.19

*Reviewers comments: the change in SF-36 is greatest in the allopurinol group. Again, one possible explanation for this may be related to the higher flare rate in febuxostat treated subjects.*

**Table 85 : Mean Change from Baseline in MOS Health Distress at the Week 24, Week 52, and Final Visits - ITT Subjects**

Domain Timepoint	Febuxostat 80 mg QD		Febuxostat 120 mg QD		Allopurinol 300 mg QD	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
<b>Health Distress</b>						
Baseline	237	79.0 (21.89)	239	79.7 (23.02)	234	77.1 (23.87)
Δ at Week 24	170	5.0 <sup>‡</sup> (21.30)	158	4.5 <sup>‡</sup> (18.23)	176	4.5 <sup>‡</sup> (19.91)
Δ at Week 52	146	7.7 <sup>‡</sup> (18.82)	140	7.0 <sup>‡</sup> (18.93)	159	9.4 <sup>‡</sup> (19.13)
Δ at Final	212	5.7 <sup>‡</sup> (21.14)	209	2.5 <sup>a</sup> (21.75)	209	7.4 <sup>‡</sup> (20.45)

All scores are on a 0-100 scale with higher scores indicating better health.

Positive change from baseline indicates improvement.

‡ Statistically significant within group change from baseline ( $p \leq 0.05$ ) using a paired t-test

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

Statistical Table 14.2.2.19

*Reviewers comments: the results of the MOS health distress are consistent with the SF-36.*

#### 4.5 Safety

The reader is referred to the review by Dr. T. Oussova.

#### 4.6 Summary and Conclusions

Trial 010 provides robust evidence of the efficacy (lowers serum urate levels in subjects with gout) of febuxostat 80 and 120 mg compared to allopurinol based on a number of analyses. Indeed, febuxostat appears to be superior to allopurinol based on the primary outcome measure as well as additional secondary measures. Conclusive evidence of the ability of febuxostat to reduce the number of gouty flares, however, has not been provided. The label should reflect the appropriate outcomes such as lowers serum urate

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### 10.1.3 Trial TMX-004

Trial 004 was a 28 day study and examined the effects of 40, 80 and 120 mg on serum uric acid levels.

One hundred fifty-three (153) subjects with hyperuricemia and gout were randomized into the study and received at least 1 dose of study drug (38 received placebo, 37 received febuxostat 40 mg QD, 40 received febuxostat 80 mg QD and 38 received febuxostat 120 mg QD). Overall, 8 (2 placebo, 1 febuxostat 40 mg QD, 3 febuxostat 80 mg QD and 2 febuxostat 120 mg QD) of the 153 subjects prematurely terminated from the study.

The most common primary reason for premature termination was adverse event (1 placebo, 1 febuxostat 40 mg QD, 2 febuxostat 80 mg QD and 2 febuxostat 120 mg QD). In addition, 1 placebo subject prematurely terminated due to gout flare and 1 febuxostat 80 mg QD subject prematurely terminated due to noncompliance with study drug dosing.

Overall, subjects ranged in age from 23 to 80 years. The mean age ranged from 52.2 to 56.2 years among all treatment groups. In all of the treatment groups, the study population was predominantly Caucasian (84%) and most subjects were male (84%). No clinically relevant differences were observed among the treatment groups for demographic characteristics. Overall, 24% of all subjects had a palpable tophus present at baseline.

Subjects were generally compliant with febuxostat dosing and similar mean compliance rates (98-106%) were noted at each visit for each treatment group. The mean number of days on study drug ranged from 27.3 to 27.9 days across the treatment groups.

As measured by either serum urate evaluation method (enzymatic or HPLC), a statistically significantly greater proportion of subjects in each febuxostat treatment group had a serum urate level <6.0 mg/dL compared to the placebo group at each visit. Across the febuxostat treatment groups, the proportion generally increased with increasing dose. The mean percent reduction in serum urate levels was also significantly greater at each visit for each febuxostat treatment group compared to the placebo group. A summary of the proportion of subjects whose serum urate level decreased to <6.0 mg/dL at the end of treatment (Day 28) is summarized by evaluation method and treatment group in Table

**Table 86 : Proportion of Subjects with Serum Urate <6.0 mg/dL at the End of Treatment - ITT Population (Study TMX-00-004)**

Method	Placebo (N=35)	Febuxostat 40 mg QD (N=34)	Febuxostat 80 mg QD (N=37)	Febuxostat 120 mg QD (N=34)
Enzymatic	0% (0/35)	56% (19/34)*	76% (28/37)*	94% (32/34)*
HPLC	3% (1/35)	82% (28/34)*	73% (27/37)*	94% (32/34)*

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

The efficacy of febuxostat in lowering serum urate levels was further confirmed with statistically significant treatment differences favoring febuxostat in mean maximum percent reductions from baseline and mean percent reductions from baseline to Day 28 in urine uric acid levels. The efficacy of febuxostat in lowering serum urate levels was also demonstrated by the proportion of subjects with serum urate levels <4.0 or <5.0 mg/dL at Day 28. Statistical significance versus placebo was achieved using Hochberg's procedure

for all febuxostat treatment groups except for 40 mg QD at the <4.0 mg/dL serum urate level.

The incidence of gout flares in the ITT population was similar between the placebo (37%) and febuxostat 40 mg QD (35%) treatment groups. Among the febuxostat treatment groups, higher flare rates were observed at higher doses (41% at 80 mg QD and 56% at 120 mg QD). However, flares were notably lower during the interval when colchicine and febuxostat were co-administered than the interval when febuxostat was administered alone (Table ).

**Table 87 : Incidence of Gout Flares During the Study (Study TMX-00-004)**

Dataset Evaluation	Placebo	Febuxostat 40 mg QD	Febuxostat 80 mg QD	Febuxostat 120 mg QD
ITT	(N=35)	(N=34)	(N=37)	(N=34)
All Gout Flares	37% (13/35)	35% (12/34)	41% (15/37)	56% (19/34)
During the Colchicine/Febuxostat Treatment Period	9% (3/33)	9% (3/33)	8% (3/36)	15% (5/34)
During the Febuxostat Treatment Period	34% (12/35)	29% (10/34)	38% (14/37)	41% (14/34)
All Subjects	(N=38)	(N=37)	(N=40)	(N=38)
All Gout Flares	37% (14/38)	35% (13/37)	43% (17/40)	55% (21/38)
Subjects with Tophi at Baseline	44% (4/9)	33% (2/6)	40% (4/10)	36% (4/11)
Subjects with Tophi at Baseline During the Colchicine/Febuxostat Treatment Period	22% (2/9)	17% (1/6)	20% (2/10)	9% (1/11)
Subjects with Tophi at Baseline During the Febuxostat Treatment Period	33% (3/9)	33% (2/6)	30% (3/10)	27% (3/11)
Subjects without Tophi at Baseline	34% (10/29)	35% (11/31)	43% (13/30)	63% (17/27)
Subjects without Tophi at Baseline During the Colchicine/Febuxostat Treatment Period	7% (2/27)	7% (2/30)	3% (1/29)	15% (4/27)
Subjects without Tophi at Baseline During the Febuxostat Treatment Period	34% (10/29)	29% (9/31)	43% (13/30)	48% (13/27)

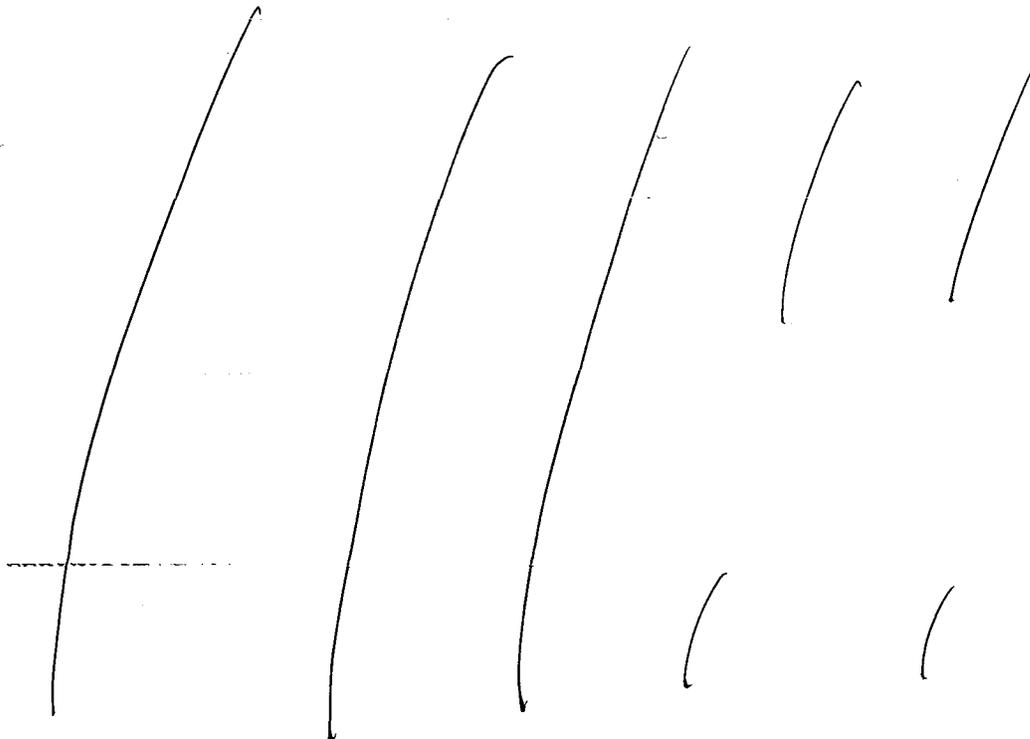
Results with respect to the primary efficacy variable summarized by subgroup (baseline serum urate levels, gender, renal function, baseline urine uric acid production and baseline tophus presence) were generally similar to the overall analysis, regardless of which serum urate evaluation method (enzymatic or HPLC) was used. Results similar to the overall analysis were also observed when the mean percent change from baseline in serum urate levels was summarized by subgroup based on baseline serum creatinine levels, baseline urine uric acid production and baseline tophus presence. There was a high correlation (r=0.97) between the enzymatic and HPLC methods used

for evaluation of serum urate levels in this study, indicating that the enzymatic method measures serum urate levels similarly to the HPLC method. The enzymatic method was used to measure serum urate levels in the Phase 3 pivotal studies.

In conclusion, this study demonstrated that each febuxostat treatment group (40 mg QD, 80 mg QD and 120 mg QD) was more effective than placebo in reducing serum urate levels at each study visit in subjects with gout. Statistical significance of febuxostat versus placebo was attained after 7 days of treatment and higher efficacy rates were generally observed with higher doses (80 mg QD and 120 mg QD) of febuxostat.

*Reviewers comments: As the 40 mg dose appears efficacious (at least in the short term), the sponsor should be asked to study the 40 mg dose further. This can be a phase IV commitment.*

## 10.2 Line-by-Line Labeling Review



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22 Page(s) Withheld

           Trade Secret / Confidential (b4)

           Draft Labeling (b4)

           Draft Labeling (b5)

           Deliberative Process (b5)

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Clinical Review  
{Schiffenbauer, Joel}  
{NDA 21-856}  
{Uloric/febuxostat}

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## References

None

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Joel Schiffenbauer  
9/12/2005 07:20:28 AM  
MEDICAL OFFICER