The results showed statistically significant difference in efficacy of all doses of febuxostat compared to placebo. The calculated lower 97.5% confidence limits also showed statistically significant superiority of febuxostat 80 mg QD by a superiority margin of 13% and by more than 13% for other doses of febuxostat. This reviewer's analysis results numerically differed slightly from those of the sponsor, but agreed on the overall conclusion.

3.1.2 STUDY # C 02-010

Title: "A Phase 3, Randomized, Multicenter Study Comparing the Safety and Efficacy of Oral Febuxostat versus Allopurinol in Subjects with Gout".

3.1.2.1 Design and Objectives

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 for randomization, followed by a 52-week double-blind treatment period.

Subjects taking allopurinol or uricosuric agents prior to the study were to discontinue them at the screening visit. These subjects were washed out of these medications for 14 days and began prophylaxis at the screening visit (Day -14) with naproxen 250 mg twice daily (BID) or colchicine 0.6 mg once daily (QD) and continued taking the medication through the day before the Week 8 visit. Eligible subjects were randomized in a 1:1:1 ratio to receive febuxostat 80 mg QD, febuxostat 120 mg QD, or allopurinol 300 mg QD. Approximately 250 subjects were to be randomized to each treatment regimen for a total of 750 randomized subjects. Subjects were evaluated at Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52.

The primary objective of this study was to compare the safety and efficacy of febuxostat versus allopurinol in subjects with gout.

3.1.2.2 Primary Efficacy Endpoint

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

3.1.2.3 Secondary Efficacy endpoints

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.

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3.1.2.4 Patients Analyzed

Intent-to-Treat (ITT) Population: The ITT population was defined as all randomized subjects who received at least one dose of study drug and had serum urate levels ≥8.0 mg/dL at Day -2 as determined by the central laboratory.

Safety Population: The safety population was defined as all randomized subjects who received at least one dose of study drug.

3.1.2.5 Disposition of Patients, Demography, and Baseline characteristics

Patients disposition is presented in Table 6 in the appendix. Seven hundred sixty subjects were randomized into the study in the US and Canada and received at least one 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.

Subject's demographic and baseline characteristics are given in Table 7 in the appendix. 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/m2 and 62% had a BMI of ≥30 kg/m2.

3.1.2.6 Sample size determination and Efficacy Analysis

3.1.2.6.1 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 one 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.

3.1.2.6.2 Primary Efficacy Analysis

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, 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. A description of Hochberg's procedure is given in Study #C02-009.

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 non-responders in the primary analysis. Subjects without post-baseline serum urate levels were not included in this analysis.

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

3.1.2.6.3 Secondary Efficacy Variables

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

Serum Urate Levels <6.0 mg/dL

The number and percentage of subjects whose serum urate levels were <6.0 mg/dL were summarized by treatment group at each visit. Pairwise comparisons between the treatment groups were made with Fisher's exact test at the Week 28, Week 52, and Final Visits. Additional analyses were conducted for subjects whose serum urate levels were <5.0 or <4.0 mg/dL at each visit. The number and percentage of subjects whose serum urate levels were <6.0 mg/dL at the Final Visit were also summarized by treatment group and baseline serum urate level. Pairwise comparisons between the treatment groups were made with Fisher's exact test within each baseline grouping.

Percent Reduction in Serum Urate Levels

The actual values and percent reduction from baseline in serum urate levels were summarized by treatment group at each visit. Pairwise comparisons between the treatment groups for the mean percent reduction values at the Week 28, Week 52, and Final Visits were made using contrast statements within the framework of a one-way ANOVA with treatment group as the factor. The baseline serum urate level was defined as the average of the Day -2 and Day 1 measurements.

Primary Tophus Size

The actual values and percent reduction from baseline in primary tophus size as determined by physical measurement were summarized by treatment group at each visit for the subset of subjects with a primary palpable tophus at the screening visit. Pairwise comparisons between the treatment groups for the percent reduction values at the Week 28, Week 52, and final visits were made using a Wilcoxon rank-sum test. An additional analysis was conducted after excluding elbow tophi. The percent reduction in primary tophus size was also summarized for subjects with an average post-baseline serum urate level <6.0 mg/dL or ≥6.0 mg/dL. If the primary tophus was no longer palpable during the 52-week double-blind treatment period, the size was assumed to be zero.

Total Number of Tophi

The actual values and reduction from baseline in the total number of tophi per subject were summarized by treatment group at each visit for the subset of subjects with palpable tophi at the screening visit. Pairwise comparisons between the treatment groups for the reduction values at the Week 28, Week 52, and final visits were made using a Wilcoxon rank-sum test. If the tophi were no longer palpable during the 52-week double-blind treatment period, the total count was assumed to be zero.

Gout Flares

The number and percentage of subjects requiring treatment for a gout flare were summarized by treatment group and time interval. Summaries were generated for flares reported before the start of treatment (prior to Day 1), during the 52-week double-blind treatment period (Day 1 to Week 52, and during and after the intended 8-week prophylaxis period (Day 1 to Week 8 and Week 8 to Week 52, respectively). Flares occurring from Week 8 to Week 52 were further summarized in 8-week intervals. Additional summaries were generated for flares occurring during and after the prophylaxis period based on each subject's actual prophylaxis dosing dates. Pairwise comparisons between the treatment groups for the percentage of subjects requiring treatment for a gout flare during the 52-week double-blind treatment period, at the last time period (Week 48 to 52), and during and after the intended and actual prophylaxis periods were made with Fisher's exact test. Separate summaries were generated for subjects with or without palpable tophi at the screening visit, by reported anatomical site, and by type of flare (monoarticular and polyarticular). The percentage of subjects requiring treatment for a gout flare was also summarized for subjects with an average post-baseline serum urate level <6.0 mg/dL or ≥6.0 mg/dL. The number of gout flares requiring treatment was summarized by treatment group using the same time intervals as for the analysis of the number of subjects requiring treatment for a gout flare. Summaries were also generated for subjects with and without palpable tophi at the screening visit. A subject who reported more than 1 gout flare during the same time interval or per anatomical site was counted only once for that time interval or anatomical site. For the summaries of the number of gout flares requiring treatment, a gout flare was counted once per onset day.

Quality-of-life Analyses

The QOL questionnaire administered during the study consisted of 2 parts. The first part included the SF-36 health survey and MOS health distress and the second included questions related to gout (GAQ).

Results from the SF-36 health survey were handled according to the SF-36 analysis manual and interpretation guide, with the exception of the SF-36 reported health transition and MOS health distress scales. Responses to the 5-point reported health transition scale were first reversed so that a higher score was indicative of better health, then were rescaled to a 0-100 scale based on the range of possible responses. If at least 2 of the 4 items in the 6-point health distress scale were available, then the scale score was calculated. In addition, the number of hours the subject was unable to leave his/her house or complete his/her responsibilities were analyzed as separate items. The actual scale scores at each visit and the change from baseline to Weeks 24 and 52 and the final visit for each scale were summarized by treatment group. Within each treatment group, the mean change from baseline to post-baseline values at each visit was tested versus zero with a one-sample paired t-test. Pairwise comparisons between the treatment groups for the mean change values at each visit were made using contrast statements within the framework of a one-way ANOVA with treatment group as the factor. Comparisons for the Treatment Satisfaction, Treatment Convenience, and Treatment Bother scales from the gout questionnaire were based on actual scale scores at each visit, since these responses were not collected at baseline.

Handling of dropouts or missing data

In order to be considered a responder in the primary efficacy analysis, each of a subject's 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 non-responder. 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 non-responders in the primary analysis. Subjects without post-baseline serum urate levels were not included in this analysis. The baseline serum urate level was defined as the average of the serum urate measurements obtained on Days -2 and 1. If a subject had a missing measurement for Day 1, the baseline was defined as the measurement taken on Day -2. For all primary and secondary efficacy analyses, missing data were not imputed.

With regard to QOL questionnaires, missing data for the SF-36™ Health Survey were handled using techniques provided in the SF-36 analysis guidelines. Furthermore, values for missing 6-point MOS Health Distress items were imputed using the mean of the available items if at least 2 of the 4 items were available. Missing data for the GAQ were not imputed.

No interim analyses were performed.

3.1.2.7 Sponsor's Results and Conclusions

3.1.2.7.1 Primary efficacy outcome

Results from the sponsor's analysis are given in Text Table 3. The proportions of subjects in the ITT population whose last 3 serum urate levels were <6.0 mg/dL were 53%, 62%, and 21% in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300 mg QD groups, respectively).

The lower 97.5% confidence limits on the differences of percentage of responders between febuxostat 80 mg QD and allopurinol 300/100 mg QD, and 120 mg QD and allopurinol 300/100 mg QD were 23% and 31%, demonstrating superiority of febuxostat 80 mg QD relative to allopurinol by a superiority margin of 23% and by 32% for febuxostat 120 mg QD. The difference between the febuxostat 80 mg QD and febuxostat 120 mg QD treatment groups was not statistically significant.

Text Table 3
Proportion of Subjects Whose Last 3 Serum Urate Levels were
<6.0 mg/dL - ITT Subjects
Study #C 02-010

Last 3 Serum Urate Levels <6.0 mg/dL	Febuxostat 80 mg QD n/N (%)		Febuxostat 120 mg QD n/N (%)		Allopurinol 300 mg QD n/N (%)	
Yes	136/255	(53%)	154/250	(62%)	53/251	(21%)
No	119/255	(47%)	96/250	(38%)	198/251	(79%)

	Difference in Proportions	97.5% CI[a]	P-value[b]
Febuxostat 80 mg vs. Allopurinol	32%	(23.1%, 41.3%)	<0.001[&]
Febuxostat 120 mg vs. Allopurinol	41%	(31.5%, 49.5%)	<0.001[&]

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

Source: Table 11.4a of sponsor's analysis

When the primary efficacy variable was summarized at the Week 28 Visit, the proportions of subjects whose last 3 serum urate levels were <6.0 mg/dL were 52%, 65%, and 20% in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300 mg QD groups, respectively. The lower 97.5% confidence limits on the differences of percentage of responders between febuxostat 80 mg QD and allopurinol 300/100 mg QD, and 120 mg QD and allopurinol 300/100 mg QD were 23% and 37%, demonstrating superiority of febuxostat 80 mg QD relative to allopurinol by a superiority margin of 23% and by 37% for febuxostat 120 mg QD. Furthermore, the response rate in the febuxostat 120 mg QD group was statistically significantly greater compared to the febuxostat 80 mg QD group. Results are given in Table 8 in the appendix.

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. In the primary analysis, these subjects were assigned as non-responders since they did not have at least 3 serum urate levels. The proportions of subjects whose last 3 serum urate levels were <6.0 mg/dL were slightly higher in this sensitivity analysis compared to the overall analysis. Among ITT subjects, response rates were 59%, 71%, and 24% in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300 mg QD treatment groups, respectively. The 97.5% confidence intervals for the differences in response rates confirmed the superiority of each febuxostat group compared to the allopurinol 300 mg QD group. The response rate in the febuxostat 120 mg QD group was statistically significantly greater compared to the febuxostat 80 mg QD group (p<0.01).

Response rates by baseline serum urate levels were lower in the allopurinol 300 mg QD treatment group compared to each of the febuxostat treatment groups. Results are given in Table 9 in the appendix.

3.1.2.7.2 Secondary Efficacy outcomes

Proportion of Subjects Whose Serum Urate Levels were <6.0 mg/dL at Each Visit

The proportions of subjects whose serum urate levels were <6.0 mg/dL were statistically significantly greater in each of the febuxostat groups compared to the allopurinol 300 mg QD group at the Week 28, Week 52, and final visits. A statistically significantly greater proportion of subjects in the febuxostat 120 mg QD group compared to the febuxostat 80 mg QD group had a serum urate level <6.0 mg/dL at the Week 28 Visit. The reduction in serum urate levels to <6.0 mg/dL was observed in all treatment groups at the Week 2 Visit and was maintained throughout treatment. Throughout the course of the study, response rates ranged from 69% to 82%, 79% to 88%, and 36% to 45% in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300 mg QD treatment groups, respectively.

Percent Reduction in Serum Urate Levels

The mean percent change from baseline in serum urate levels was statistically significantly different between each of the febuxostat groups and the allopurinol 300 mg QD treatment group at the Week 28, Week 52, and Final Visits, with greater mean decreases observed in each of the febuxostat groups compared to the allopurinol 300 mg QD group. In addition, statistically significant differences were observed between the febuxostat treatment groups at the Week 28, Week 52, and final visits, with greater mean decreases observed in the febuxostat 120 mg QD group compared to the febuxostat 80 mg QD group. The percent reduction in serum urate levels was observed in all treatment groups at the Week 2 visit and was maintained throughout treatment. Throughout the course of the study, mean percent changes from baseline ranged from -45% to -49%, -52% to -57%, and -33% to -37% in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300 mg QD treatment groups, respectively.

Percent Reduction in Primary Tophus Size Determined by Physical Measurement Among Subjects with a Primary Palpable Tophus at Baseline

Among subjects with a primary palpable tophus at baseline, there were no statistically significant differences between treatment groups for the percent change from baseline in primary tophus size at the Week 52 or final visits. The percent change from baseline in primary tophus size was statistically significantly different between the febuxostat 120 mg QD group and both the febuxostat 80 mg QD and allopurinol 300 mg QD treatment groups at the Week 28 Visit. Subjects in the febuxostat 120 mg QD group had greater percent decreases from baseline in primary tophus size compared to the febuxostat 80 mg QD and allopurinol 300 mg QD treatment groups at the Week 28 visit. In each treatment group, there was a trend toward larger median percent changes from baseline over time. The median percent change from baseline at Week 52 was -83.4%, -65.5%, and 49.7% in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300 mg QD treatment groups, respectively.

Percent Reduction in Primary Tophus Size Excluding Elbow Locations Determined by Physical Measurement Among Subjects with a Primary Palpable Tophus at Baseline

Change in tophus size was evaluated excluding elbow tophi due to the variability in measurements occurring at that site, which may be due to olecranon bursal fluid. Among subjects with a primary palpable tophus at baseline, there were no statistically significant differences between treatment groups for the percent change from baseline in primary tophus size (excluding elbow locations) at the Week 28 or final visits. The percent change from baseline in primary tophus size (excluding elbow locations) was statistically significantly different between the febuxostat 80 mg QD and allopurinol 300 mg QD treatment groups at the Week 52 visit. Subjects in the febuxostat 80 mg QD group had greater percent decreases from baseline in primary tophus size compared to the allopurinol 300 mg QD treatment group at the Week 52 visit. The median percent change from baseline at Week 52 was -87.0%, -72.5%, and -28.7% in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300 mg QD treatment groups, respectively.

Percent Reduction in Primary Tophus Size by Average Post-baseline Serum Urate Level Among Subjects with a Primary Palpable Tophus at Baseline

Among subjects with a primary palpable tophus at baseline, the median percent change from baseline in primary tophus size was numerically greater in the group that achieved an average post-baseline serum urate level <6.0 mg/dL compared to the group that achieved an average post-baseline serum urate level ≥6.0 mg/dL. At Week 52, the median percent change from baseline in primary tophus size was -75.0% in the group of subjects that achieved an average post-baseline serum urate level <6.0 mg/dL compared to -49.7% in the group of subjects that achieved an average post-baseline serum urate level ≥6.0 mg/dL.

Reduction in Total Number of Tophi Among Subjects with Palpable Tophi at Baseline

Among subjects with palpable tophi at baseline, no statistically significant differences were observed between treatment groups in the change from baseline in number of tophi at the Week 28, Week 52, and final visits. In each treatment group, there was little change in median values over time. A decrease in the mean number of tophi was noted over time in each treatment group and the mean change from baseline at Week 52 was -0.4, -1.0, and -0.7 tophi in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300 mg QD treatment groups, respectively.

Proportion of Subjects Requiring Treatment for a Gout Flare

The majority of subjects in each treatment group received treatment for a gout flare during the study, with similar percentages reported by subjects in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300 mg QD treatment groups (64%, 72%, and 65%, respectively). Similar percentages of subjects had flares requiring treatment during the screening period before study drug had been started (8% to 11% across treatment groups). During the intended 8-week prophylaxis period (Day 1 to Week 8), a statistically significantly greater proportion of subjects in the febuxostat 120 mg QD (36%) treatment group required treatment for a gout flare compared to both the febuxostat 80 mg QD (22%) and allopurinol 300 mg QD (21%) 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 were observed between treatment groups either after the intended 8-week prophylaxis period (Week 8 to Week 52) or during the 52-week double-blind treatment period (Day 1 to Week 52). During the 8-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 48 to Week 52) in the febuxostat 80 mg QD and febuxostat 120 mg QD groups (8% and 6%, respectively) compared to the allopurinol 300 mg QD group (11%), although these differences were not statistically significant.

Proportion of Subjects Requiring Treatment for a Gout Flare by Average Post-baseline Serum Urate Level

The proportion of subjects requiring treatment for a gout flare was numerically lower during the last 4 weeks of the study (Week 48 to Week 52) among the group of subjects that achieved an average post-baseline serum urate level <6.0 mg/dL compared to the group of subjects that achieved an average post-baseline serum urate level ≥6.0 mg/dL (6% vs. 14%). Similar to the overall profile, in both groups of subjects, the overall incidence of subjects requiring treatment for a gout flare decreased over time.

Quality-of-life Results

Short Form-36 Health Survey

There were no statistically significant differences between the treatment groups at the Week 24 visit for any SF-36 component and improvements from baseline were generally similar. The allopurinol 300 mg QD treatment group had statistically significantly greater improvements than the febuxostat 120 mg QD treatment group at the final visit in physical functioning, general health, vitality, social functioning, role-emotional, reported health transition, PCS, and MCS. With the exception of social functioning, these differences were not statistically significant at the Week 52 visit. Additionally, the allopurinol 300 mg QD treatment group had statistically significantly greater improvements than the febuxostat 80 mg QD treatment group at the final visit in physical functioning and role-emotional. These comparisons were not statistically significant at the Week 52 visit. At the Week 52 visit, the febuxostat 120 mg QD treatment group had greater improvement than the febuxostat 80 mg QD treatment group in bodily pain and the febuxostat 80 mg QD treatment group had greater improvement than the febuxostat 120 mg QD treatment group in social functioning.

11.4.1.3.2 Medical Outcomes Study Health Distress Scale

There were no statistically significant differences between the treatment groups at the Week 24 or Week 52 visits in MOS health distress. The allopurinol 300 mg QD treatment group had a statistically significantly greater improvement than the febuxostat 120 mg QD treatment group at the final visit in MOS health distress.

Gout Assessment Questionnaire

Statistically significant improvements from baseline were observed in each treatment group at the Week 24, Week 52, and final visits in the following components of the GAQ: gout concern, gout pain and severity, gout flare symptom interference, well-being, productivity, and hours unable to leave home.

There were no statistically significant differences between the treatment groups at the Week 52 visit in any of the GAQ domains and the improvements were generally similar between the treatment

groups. There were also no statistically significant differences between the treatment groups at the Week 52 visit for the hours unable to leave home or the hours unable to work. Improvements in the hours unable to leave home were greater for the febuxostat 80 mg QD and allopurinol 300 mg QD treatment groups than for the febuxostat 120 mg QD treatment group. Improvements in the hours unable to work were greater for the febuxostat 80 mg QD treatment group than for the febuxostat 120 mg QD and allopurinol 300 mg QD treatment groups.

The allopurinol 300 mg QD treatment group had statistically significantly greater improvements than the febuxostat 120 mg QD treatment group in gout concern and gout pain and severity at the final visit. The allopurinol 300 mg QD treatment group had statistically significantly greater mean values for treatment satisfaction than in each of the febuxostat treatment groups at the Week 24 visit. Additionally, the allopurinol 300 mg QD treatment group had statistically significantly greater mean values for treatment satisfaction and treatment bother than the febuxostat 120 mg QD treatment group at the final visit. Subjects in the febuxostat 80 mg QD treatment group had statistically significantly greater improvement than the febuxostat 120 mg QD treatment group in gout concern and hours unable to leave home at the final visit in addition to greater mean values for treatment satisfaction.

3.1.2.8 Reviewer's Findings and Conclusions

To verify the sponsor's analysis this reviewer reanalyzed the primary efficacy variable. This reviewer analyzed the data of all patients with observations up to 52 weeks as the primary analysis. In addition, to evaluate the sensitivity of the analysis this reviewer also analyzed the data all patients with all observations and 52 weeks completers. Also to make a comparison with Study #C 02-009 a fourth population of all patients with observations up to 28 week was analyzed. Text Table 4 shows this reviewer's analysis.

Text Table 4
*P-values Comparing Responders in Febuxostat and Placebo and
97.5% Confidence Intervals on difference of Percentage of Responders Between
Febuxostat and Allopurinol
Study # C 02-010

Population	Treatment	N	Responder	Percent	97.5 % C. I.
All patients	FEBUXOSTAT 120 MG QD	251	138	55	26 - 45
All observations	FEBUXOSTAT 80 MG QD	256	128	50	21 - 40
	ALLOPURINOL 300 MG QD	253	50	20	
All patients	FEBUXOSTAT 120 MG QD	251	139	55	26 - 45
Observations up to Week 52	FEBUXOSTAT 80 MG QD	256	131	51	22 - 41
regardless if patients completed 52 weeks	ALLOPURINOL 300 MG QD	253	50	20	
52 weeks completers	FEBUXOSTAT 120 MG QD	153	110	72	35 - 58
Observations up to 52 weeks	FEBUXOSTAT 80 MG QD	168	102	61	23 - 47
	ALLOPURINOL 300 MG QD	187	48	26	
All patients	FEBUXOSTAT 120 MG QD	251	156	62	34 - 50
Observations up to Week 28	FEBUXOSTAT 80 MG QD	256	132	52	24 - 40
	ALLOPURINOL 300 MG QD	253	51	20	

* All p-values comparing febuxostat and allopurinol or comparing febuxostat and placebo were <0.0001.

For 52 weeks data the calculated lower 97.5% confidence limits showed superiority of febuxostat 80 mg QD in efficacy relative to allopurinol by a superiority margin of 22% and by 26% for febuxostat 120 mg QD. Twenty eight weeks data demonstrated a superiority of febuxostat 80 mg QD relative to allopurinol by a superiority margin of 24% and by 34% for febuxostat 120 mg QD.

3.1.3 STUDY # TMX-00-004

Title: "Phase 2, Dose-Response, Safety and Efficacy Study of Oral Febuxostat (TMX-67) in Subjects with Gout".

3.1.3.1 Design and Objectives

This was a Phase 2 randomized, double blind, placebo-controlled, parallel-group, multicenter study with a 2-week washout/run-in period and a 4-week treatment period. One hundred twenty healthy male and female subjects were enrolled.

Subjects who were taking allopurinol or uricosuric agents discontinued them at the screening visit. Subjects were washed off of these medications for 2 weeks. Subjects who were not receiving allopurinol or uricosuric agents started a 2-week run-in period prior to begin prophylactic treatment with colchicine. All subjects began treatment with colchicine 0.6 mg BID and continued for 4 weeks, stopping the day before the Day 14 visit (Day 13). The purpose of the colchicine treatment was to decrease the incidence of gout flares during the 2-week washout/run-in period and during the first 2 weeks of the double-blind treatment period.

Qualified subjects with serum urate levels ≥8.0 mg/dL entered the double-blind treatment period and were randomly assigned to 1 of the 4 treatment groups:

Group A: Placebo to match febuxostat QD (6 placebo tablets)
Group B: Febuxostat 40 mg QD (2 x 20 mg febuxostat + 4 placebo tablets)
Group C: Febuxostat 80 mg QD (4 x 20 mg febuxostat + 2 placebo tablets)
Group D: Febuxostat 120 mg QD (6 x 20 mg febuxostat)

Double-blind treatment visits occurred on Days 7, 14, 21 and 28. Subjects who completed the 4 week treatment period were given the option of enrolling into a 52-week open-label study of febuxostat (Protocol No. TMX-01-005).

The objective of this study was to select oral dose(s) of febuxostat, which safely and effectively decrease serum urate levels in subjects with gout.

3.1.3.2 Primary Efficacy Endpoint

The primary efficacy variable was "success" rate, defined as the proportion of subjects whose serum urate level decreased to <6.0 mg/dL after treatment with study drug (Day 28). Serum urate levels were evaluated by 2 methods during the study. One sample was measured at the central laboratory using an enzymatic method and the second sample was measured by a specialty laboratory using a high-pressure (performance) liquid chromatography (HPLC) method.

3.1.3.3 Secondary Efficacy endpoint

The secondary efficacy variables included the proportion of subjects whose serum urate level decreased to <6.0 mg/dL after treatment with the study drug by Days 7, 14 and 21; the percent reduction in serum urate levels from baseline to Days 7, 14, 21 and 28; the maximum percent reduction in serum urate level from baseline during the entire treatment period; and the percent reduction in 24-hour urine uric acid level from baseline to Day 28. Other efficacy variables included the incidence of gout flares, the changes in joint x-ray abnormalities from baseline to Day 28 and components of the QOL questionnaires.

3.1.3.4 Patients Analyzed

Intent-to-Treat (ITT) Population: The ITT population was defined as all randomized subjects who had a serum urate level of ≥8.0 mg/dL (using the enzymatic method) on Day -2.

Safety Population: Safety population was defined as all randomized subjects who received at least one dose of study drug.

3.1.3.5 Disposition of Patients, Demography, and Baseline characteristics

Table 10 in the appendix presents the disposition of all randomized subjects. One hundred fifty-three (153) subjects were randomized into the study and received at least one 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 due to an adverse event (1 placebo, 1 febuxostat 40 mg QD, 2 febuxostat 80 mg QD and 2 febuxostat 120 mg QD).

Summary of demographic and baseline characteristics is given in Table 11 in the appendix. 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 significant differences were observed among the treatment groups for demographic characteristics. Among the subjects who had 24-hour urine uric acid levels collected at baseline, the majority (79%) was categorized as under-excretors of uric acid (urine uric acid ≤800 mg/day), while 21% were categorized as overproducers of uric acid (urine uric acid >800 mg/day). Results were similar across the treatment groups. Overall, 24% of all subjects had a palpable tophus present at baseline.

3.1.3.6 Sample size determination and Efficacy Analysis

3.1.3.6.1 Determination of sample size

Sample size considerations were based on having good power to detect a statistically significant difference between each of the febuxostat dose groups and placebo in the proportion of success. It was estimated that 23 subjects per treatment group would provide at least 90% power to be able to detect a difference between febuxostat dose group and placebo with a two sided significance level of 0.05. This assumes an 80% responder rate for any of the febuxostat dose groups and 30% for placebo. One hundred twenty (120) subjects were enrolled in this study with 30 subjects per treatment group to allow for a dropout rate of approximately 20%.

3.1.3.6.2 Primary Efficacy Analysis

The "success" rates were summarized and compared between each of the febuxostat treatment groups and placebo using Fisher's exact test. The pairwise comparisons were made using Hochberg's procedure, where the 3 pairwise p-values were ordered from smallest to largest and the largest p-value was compared to 0.049. If the largest pairwise p-value was less than or equal to 0.049, then all 3 comparisons were considered statistically significant. If the largest pairwise p-value was greater than 0.049, then the second largest pairwise p-value was compared to 0.049/2=0.0245. If the second largest pairwise p-value was less than or equal to 0.0245, the remaining comparisons were considered statistically significant. If the second largest pairwise p-value was greater than 0.0245 then the third largest pairwise p-value was compared to 0.049/3=0.0163 and the procedure continued as described above. Similar analyses were conducted for the proportion of subjects whose serum urate level decreased to <4.0 mg /dL and <5.0 mg g/dL by Day 28.

9.7.1.4.2 Secondary Efficacy Variables

Fisher's exact test was used to compare the proportion of subjects whose serum urate level decreased to <6.0 mg /dL at Days 7, 14 and 21. Adjustments for multiple comparisons were made using Hochberg's procedure. The percent reduction in serum urate levels from baseline to each of the study visits was summarized by treatment group using descriptive statistics and the treatment groups were compared with a one way analysis of variance (ANOVA) model with treatment group as the factor. In addition, pairwise comparisons using the t-test were performed between placebo and each of the febuxostat treatment groups. Adjustments for multiple comparisons were made using Hochberg's procedure. Similar analyses were performed using the maximum percent reduction and the 24-hour urine uric acid level. The percent reduction in serum urate levels from baseline to Day 28 was also summarized by baseline creatinine levels <1.0 mg/dL, 1.0-1.5 mg/dL, >1.5 mg/dL), baseline urine uric acid production and baseline tophus presence. In addition, the incidence of gout flares during the study for all randomized subjects and for all ITT subjects was summarized overall and by severity by treatment group. Separate summaries were generated for gout flares reported during the colchicine/ febuxostat and febuxostat only treatment periods and for subjects with and without tophi at baseline.

9.7.1.4.3 Quality-of-life Analyses

The QOL questionnaire was administered on Day 1 and at the end of the study (Day 28) or premature termination. The questionnaire used in this study was a combination of 2 parts. The first part included the SF-36 questionnaire and the second included questions related to gout, with a separate analysis performed for each part. For each part, baseline was defined as the score on Day 1 and post-dose was defined as the score on Day 28. Subjects who prematurely terminated from the study were not included in this analysis. The SF-36 questionnaire data were handled according to the SF-36 analysis manual and interpretation guide.

Part I: SF-36 questionnaire:

For each scale, a transformed score was computed separately for Day 1 and Day 28. Descriptive statistics were estimated for the baseline, post-dose and change from baseline to post-dose score. Also, a one-way ANOVA was performed for the change from baseline to post-dose score for each scale with treatment group as the factor. Each of the febuxostat treatment groups was compared to placebo using the appropriate pairwise contrast within the ANOVA model. Within treatment group changes were analyzed using paired t-tests.

Part II: Gout Questionnaire:

This part contained 7 items for Day 1 and 12 items for Day 28. For each item, descriptive statistics were computed for baseline, post-dose and change from baseline to post-dose for those items that had both a baseline and a post-dose value. Similar analyses as described above in Part I were performed for the changes from baseline to post-dose.

3.1.3.6.3 Handling of dropouts or missing data

The last observation carried forward (LOCF) method was used to impute missing data for the primary and secondary efficacy variables. The baseline values were carried forward to subsequent visits if necessary.

3.1.3.6.4 Interim analysis

An interim analysis of the serum urate and safety data was conducted for 122 subjects who had completed the study by June 15, 2001. It was expected that enrollment would be nearly completed by that date. The objective of this administrative look was to facilitate the dose selection process for formulation development and initiation of the Phase 3 program. The analysis was conducted by a designated third party that did not have any involvement in the study conduct or any study activity. The data entry and database management proceeded without knowledge of the individual subject's treatment assignment. Upon resolution of the relevant queries, the randomized treatment codes were released to the third party. The results of the analysis were summarized by treatment groups, while not identifying the individual subject's treatment assignment. Accordingly, the alpha expended for the interim analysis was 0.001, thus the Type I error rate adjustment was made from 0.05 to 0.049 in the final analysis of this study.

3.1.3.7 Sponsor's Results and Conclusions

3.1.3.7.1 Primary efficacy outcome

A summary of the success rates at the end of treatment is summarized by evaluation method and treatment group in Text Table 5. As measured by either serum urate evaluation method at the completion of treatment, a statistically significant greater proportion of subjects in each febuxostat treatment group had a serum urate level of <6.0 mg/dL compared to the placebo group. Within the febuxostat treatment groups, the proportion generally increased with increasing dose.

Text Table 5
Success Rates (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.
Cross Reference: Statistical Table 14.2.1.1 and Appendices 16.2-6.1.1 and 16.2-6.1.2.
Source: Table 11.4a of sponsor's analysis

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3.1.3.7.2 Secondary Efficacy outcomes

Success Rates at Each Visit

Statistically significant greater proportions of subjects in each febuxostat treatment group (compared to the placebo group) had a serum urate level of <6.0 mg/dL at each visit (Days 7, 14 and 21) as determined by either serum urate evaluation method.

Percent Reduction in Serum Urate Levels from Baseline at Each Visit

The mean percent reduction from baseline in serum urate level, a secondary efficacy variable, differed among febuxostat treatment groups at each visit, with the greatest percent reduction seen in the 120 mg QD group. Nevertheless, each febuxostat treatment group showed a statistically significantly greater percent reduction from baseline urate level (compared with the placebo group) at each visit (Days 7, 14, 21 and 28). Results similar to the overall analysis were observed when the mean percent change from baseline to Day 28 in serum urate levels was summarized by subgroup based on baseline serum creatinine levels.

Maximum Percent Reduction in Serum Urate Levels from Baseline During the Entire Treatment Period

The maximum percent reduction in serum urate levels from baseline during the entire treatment period was statistically significantly greater in each of the febuxostat treatment groups compared to the placebo group. Mean maximum percent reductions from baseline ranged from 42.53% to 62.78% among the febuxostat treatment groups and 9.99% in the placebo group using the enzymatic method. A similar pattern was observed when the HPLC method was used, with mean maximum percent reductions from baseline ranging from 41.41 to 61.31% among the febuxostat treatment groups and 11.34% in the placebo group. The differences between each febuxostat treatment group and placebo were statistically significant (p<0.001).

Incidence of Gout Flares During the Study

Among ITT subjects, the incidence of gout flares was similar between the placebo and febuxostat 40 mg QD treatment groups (37% and 35%, respectively). Among the febuxostat treatment groups, higher flare rates were noted with increasing dose, with 35%, 41% and 56% of subjects in the febuxostat 40 mg QD, 80 mg QD and 120 mg QD treatment groups, respectively, having a gout flare during the study. The most frequent anatomic location cited for a gout flare was the toe, which was reported by 20% to 26% of subjects in each treatment group.

Quality-of-life Results

Sporadic statistically significant differences were observed between one or more of the febuxostat groups and the placebo group in various QOL variables. However, no specific trend was apparent; this may be due to the short treatment period of 4 weeks.

3.1.3.8 Reviewer's Findings and Conclusions

As mentioned before, this was a short term 4-weeks study compared to more than 28 weeks for Studies #C02-009 and #C02-010. Also the sample size of this study was very small compared to Studies #C02-009 and #C02-010. The sponsor did not claim it to be a pivotal study. Because of the

above reasons this reviewer did not consider this study as significant in contributing toward the proof of efficacy of the study drug and hence did not perform any re-analysis of the data.

3.1.4 STUDY # C 02-021

Title: "A Phase 3, Open-Label, Randomized, Allopurinol-Controlled Study to Assess the Long-Term Safety of Oral Febuxostat in Subjects with Gout".

3.1.4.1 Design and Objectives

This was a Phase 3, open-label, multicenter, randomized, allopurinol-controlled, 24-month, safety extension of Studies #C02-009 and #C02-010. Up to 1500 subjects who had completed the Phase 3, 28-week, double-blind, placebo and allopurinol-controlled study (Study C02-009) or the Phase 3, 52-week, double-blind, randomized, allopurinol-controlled study (Study C02-010) were eligible for entry into this long-term extension study. In these previous studies the site staff had been blinded as to the serum urate levels, in order to maintain the study treatment blind. In this study, the site staff was unblinded to the serum urate levels after Visit 2/End of Month 1. This study is ongoing and expected to continue so that all subjects will have 24 months of treatment. This interim analysis was prepared with data contained in the clinical database up to and including 30 April 2004.

The original study protocol was for a single-arm study in which all subjects received febuxostat 80 mg QD, with the option to titrate to febuxostat 120 mg QD. Based on a request from the FDA to include an active comparator arm in order to provide more robust safety data, Protocol Amendment #2 which added an allopurinol treatment group and randomization to treatment groups, was implemented. Subjects were randomized in a 2:2:1 ratio to receive febuxostat 80 mg, febuxostat 120 mg, or allopurinol 300/100 mg once daily (dose depended on the subject's serum creatinine concentration at the study visit prior to the final visit of the previous study). The final visit for Study #C02-009 (Week 28/Visit 13) or Study #C02-010 (Week 52/Visit 17) was considered Day 1/Visit 1 assessments for this study.

Subjects who were enrolled prior to Protocol Amendment #2 were assigned initially to a treatment group of febuxostat 80 mg QD with an option to titrate to febuxostat 120 mg QD; these subjects could not be switched to an allopurinol, but the febuxostat dose could be adjusted as follows:

- Subjects who received febuxostat 80 mg QD could be titrated up to 120 mg QD if the subject's serum urate level was ≥6.0 mg/dL.
- Subjects who received febuxostat 120 mg QD could be titrated down to 80 mg QD to maintain the subject's serum urate level between ≥3.0 mg/dL and <6.0 mg/dL.

Subjects enrolled after the implementation of Protocol Amendment #2 were randomized in a 2:2:1 ratio to receive either febuxostat 80 mg QD, febuxostat 120 mg QD, or allopurinol (100 mg QD for subjects with serum creatinine >1.5 mg/dL and ≤2.0 mg/dL at the study visit prior to the last visit of the previous study or 300 mg QD for subjects with serum creatinine ≤1.5 mg/dL at the study visit prior to the last visit of the previous study). Between Visit 2/End of Month 1 and the beginning of Visit 5/End of Month 6, subjects randomized to receive febuxostat 80 mg QD could be titrated upward to febuxostat 120 mg QD or downward from febuxostat 120 mg QD to febuxostat 80 mg QD in order to maintain the subject's serum urate level between ≥3.0 mg/dL and <6.0 mg/dL.

Specifically:

- Subjects randomized to receive febuxostat 80 mg QD could be switched to allopurinol following the occurrence of an adverse event or following sponsor-approved, investigator recommendation.
- Subjects randomized to receive febuxostat 120 mg QD could be switched to allopurinol if the serum urate was ≥6.0 mg/dL, if an adverse event occurred, or if sponsor-approved, investigator recommendation was obtained. If a subject's serum urate level remained ≥6.0 mg/dL after a switch to allopurinol therapy, the subject was discontinued.
- Subjects randomized to receive allopurinol could be switched to febuxostat 80 mg QD if the serum urate was ≥6.0 mg/dL, if an adverse event occurred, or if sponsor-approved, investigator recommendation was obtained. After a switch to febuxostat 80 mg QD, dose titration to febuxostat 120 mg QD was permitted in order to maintain the subject's serum urate level between ≥3.0 mg/dL and <6.0 mg/dL. If a subject's serum urate level remained ≥6.0 mg/dL after receiving febuxostat 120 mg QD, the subject was discontinued.

The objective of this study was to evaluate the long-term safety of febuxostat 80 mg QD and febuxostat 120 mg QD in subjects with gout, as compared to allopurinol.

3.1.4.2 Primary Efficacy Endpoint

The primary efficacy variable was the proportion of subjects whose serum urate level decreased to or was maintained at <6.0 mg/dL (success).

3.1.4.3 Secondary Efficacy endpoint

For this interim analysis the secondary variables were 1) The percent reduction in serum urate levels and 2) The proportion of subjects requiring treatment for a gout flare.

3.1.4.4 Patients Analyzed

Primary efficacy population: All enrolled subjects who received at least one dose of study drug were included in the efficacy analyses.

Safety Population: All randomized subjects in the study.

3.1.4.5 Disposition of Patients, Demography, and Baseline characteristics

As of the 30 April 2004 cut-off date, a total of 1074 subjects had received at least one dose of study drug and were included in this interim analysis. Prior to Protocol Amendment #2, 355 subjects were enrolled into the study and after the implementation of Protocol Amendment #2, an additional 719 subjects were enrolled into the study. The number of subjects initially assigned to febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups were 650, 282, and 142, respectively. Table 12 summarizes subject disposition and reasons for premature discontinuation at the interim cut-off date.

All subjects who entered this study had received treatment previously in Study #C02-009 or Study #C02-010. The demographic data and baseline characteristics for subjects entering this study were defined as the last observation obtained prior to receiving the first dose of study drug in either Study

#C02-009 or Study #C02-010, and are summarized by initial treatment assignment in this study in Table 13 in the appendix.

No significant or clinically relevant differences across treatment groups were observed for any baseline characteristics. The demographics of the subjects who participated in this study were typical for a gout population, with the majority of the study subjects being Caucasian (>76%), male (>94%), with a mean age of 51 years, and a mean weight of more than 220 pounds.

Treatment assignments for this study were summarized by the treatment received in prior studies (Study #C02-009 or Study #C02-010) and are presented in Table 14 in the appendix.

For all subjects in this interim analysis, the distribution of initial treatment assignments and the number of subjects who took at least one dose of febuxostat 80 mg QD, febuxostat 120 mg QD, or allopurinol 300/100 mg QD are shown in Table 15 in the appendix. Prior to the implementation of Protocol Amendment #2, subjects could only switch between the febuxostat 80 mg QD and febuxostat 120 mg QD treatment groups.

After the implementation of Protocol Amendment #2, subjects could also switch to allopurinol. A summary of first treatment changes for subjects enrolled after Protocol Amendment #2 is provided in Table 16 in the appendix. Overall, the percentages of subjects who enrolled after the implementation of Protocol Amendment #2 and changed from initial treatment (or dose) were 12%, 17% and 35% for febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD, respectively. Of the subjects initially treated with allopurinol, 35% (49/142) changed to a febuxostat treatment group and only 3% (17/577) of subjects initially treated with either febuxostat dose changed to the allopurinol treatment group. For subjects who enrolled under Protocol Amendment #2, the reasons subjects changed treatment groups are summarized in Table 17 in the appendix.

Overall, the proportion of subjects who initially changed treatment due to serum urate level >6.0 mg/dL were 8%, 5%, and 31% for febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups, respectively. Twenty subjects (7%) taking febuxostat 120 mg QD changed treatment due to serum urate levels <3.0 mg/dL. No subject had a serum urate level less than 1.0 mg/dL. There were no such changes noted for febuxostat 80 mg QD or allopurinol 300/ 100 mg QD treatment groups. The proportion of subjects who changed treatment, due to adverse event or other reasons, was low and approximately the same across the 3 treatment groups.

3.1.4.6 Sample size determination and Efficacy Analysis

3.1.4.6.1 Determination of sample size

In this multicenter, open-label study, all subjects who completed Study #C02-009 or Study #C02-010 were eligible to enroll (up to 1500 subjects). No formal sample size calculations were performed.

3.1.4.6.2 Primary Efficacy Analysis

For this interim analysis, the proportion of subjects with a serum urate level <6.0 mg/dL was summarized by assigned treatment for all visits where scheduled serum urate levels were obtained, up to a subject's first treatment change. Similar summaries were performed for subjects whose serum urate levels <5.0 mg/dL and <4.0 mg/dL. The proportion of subjects with a serum urate level <6.0 mg/dL also was summarized by the serum urate level response (<6.0 mg/dL or ≥6.0 mg/dL in the

previous study (Study C02-009 or Study C02-010). Similarly, the proportion of subjects with a serum urate level <6.0 mg/dL was summarized before and after the first treatment change.

3.1.4.6.3 Secondary Efficacy Analysis

Percent Reduction in Serum Urate Levels from Baseline

Summary statistics were generated for the percent reduction in serum urate levels from baseline by assigned treatment for all visits where scheduled serum urate levels were obtained, up to a subject's first treatment change. For subjects who participated in Study #C02-009, baseline was considered the average of the serum urate measurements within the baseline window (Days -10 to 1 from said study). If a subject had more than 3 measurements within the baseline window, the last 3 measurements were used. For subjects who participated in Study #C02-010, baseline was considered the average of the Study #C02-010 Day -2 and Day 1 serum urate measurements.

Gout Flares

The proportion of subjects requiring treatment for a gout flare were summarized by day of onset (overall, ≤1 month, >1 to 2 months, >2 to 6 months, and >6 months) for all subjects and by the last treatment received prior to the gout flare. The last treatment received was considered the dose and treatment that the subject was taking at the time of a gout flare. A subject reporting more than 1 gout flare during the same time interval was counted once for that time interval for the overall summary and once per treatment for the summary by last treatment received.

3.1.4.6.4 Handling of dropouts or missing data

All serum urate values collected from the start of the study to within 3 days following a subject's final dose were included in the efficacy analyses. Missing values were not imputed. Subjects missing a value for an analysis at a given time point were not included in the analysis.

3.1.4.7 Sponsor's Results and Conclusions

3.1.4.7.1 Primary efficacy outcome

The proportion of subjects with serum urate levels <6.0 mg/dL up to first treatment change by visit are shown in Text Table 6.

At Month 1, the proportion of subjects whose serum urate levels were <6.0 mg/dL were 81%, 86%, and 47% in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups, respectively. At Month 4, these rates were 81%, 82%, and 50% in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups, respectively. At Months 2 and 4, similar reductions were maintained in each treatment group. For visits at Month 6 and 8 data from treatment groups febuxostat 120 mg QD and allopurinol 300/100 mg were not available.

Text Table 6
Proportion of Subjects with Serum Urate Levels <6.0 mg/dL up to
First Treatment Change by Visit
Study #C02-021

Visit (End of Month)	Febuxostat 80 mg QD N=649 % (n/N)	Febuxostat 120 mg QD N=283 % (n/N)	Allopurinol 300/100 mg QD N=143 % (n/N)
Month 1	81 (496/613)	86 (229/265)	47 (64/137)
Month 2	79 (423/537)	80 (157/196)	47 (45/96)
Month 4	81 (295/366)	82 (71/87)	50 (17/34)
Month 6	83 (124/150)	-	-
Month 8	78 (7/9)	-	-

Cross-reference: Statistical Table 14.2.1 and Appendix 16.2.6.1.1

Source: Table 11.4a of sponsor's analysis

Reviewer's comment: In the 28 weeks result of Study # C02-009 and 52 weeks result of Study #C02-010, the allopurinol responder rate was under half of the febuxostat responder rate. In this study, after 4 months the allopurinol responder rate is more than half of the febuxosat responder rate. It will be interesting to see difference between these responder rates at the end of this study.

3.1.4.7.2 Secondary Efficacy outcome

Proportion of Subjects with Serum Urate Levels <5.0 mg/dL and <4.0 mg/dL

At Month 1, the proportion of subjects whose serum urate levels were <5.0 mg/dL were 58%, 71%, and 18% in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups, respectively. At Month 4, the proportion of subjects whose serum urate levels were <5.0 mg/dL were 54%, 70%, and 18% in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups, respectively.

Similarly, at Month 1, the proportion of subjects whose serum urate levels were <4.0 mg/dL were 25%, 44%, and 1% in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups, respectively. At Month 4, the proportion of subjects whose serum urate levels were <4.0 mg/dL were 24%, 40%, and 3% in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups, respectively.

Percent Change in Serum Urate Level from Baseline up to First Treatment Change by Visit

A mean percent decrease in serum urate levels was demonstrated for all treatment groups. However, subjects treated with febuxostat 80 and 120 mg QD demonstrated larger percent decreases from baseline than subjects treated with allopurinol 300/100 mg QD. Subjects treated for 4 months with febuxostat 80 mg QD showed mean percent decreases of approximately 49% and subjects treated with febuxostat 120 mg QD showed mean decreases of approximately 52%, and subjects treated with allopurinol showed mean decreases of approximately 36% through 4 months.

Subjects Requiring Treatment for a Gout Flare

Overall, the percentage of subjects requiring treatment for gout flare was similar for the febuxostat treatment groups and slightly lower for subjects treated with allopurinol. Anti-inflammatory agents

such as NSAIDs and colchicine were the most frequently prescribed medications across the treatment groups to treat the gout flare.

3.1.4.8 Reviewer's Findings and Conclusions

Since this was an incomplete long term safety extension of Studies #C2-009 and #C2-010, and the sponsor did not claim it as a proof of efficacy study, this reviewer did not perform any re-analysis of the data.

3.2 EVALUATION OF SAFETY

3.2.1 SPONSOR'S ANALYSIS OF SAFETY DATA

3.2.1.1 Study # C02-009

Summary of patients with at least one adverse event during treatment is given in Table 18 in the appendix. Of the 1072 randomized subjects who received study drug, 97 (72%) subjects in the placebo group, 181 (68%) subjects in the febuxostat 80 mg QD group, 183 (68%) subjects in the febuxostat 120 mg QD group, 98 (73%) subjects in the febuxostat 240 mg QD group, and 200 (75%) subjects in the allopurinol 300/100 mg QD group reported at least one adverse event during treatment. Thirty-one (23%) subjects in the placebo group, 56 (21%) subjects in the febuxostat 80 mg QD group, 49 (18%) subjects in the febuxostat 120 mg QD group, 39 (29%) subjects in the febuxostat 240 mg QD group, and 44 (16%) subjects in the allopurinol 300/100 mg QD group reported at least one adverse event that was considered by the investigator to be possibly, probably, or definitely treatment-related. The differences between the febuxostat 240 mg QD and each of the febuxostat 120 mg QD and allopurinol 300/100 mg QD treatment groups were statistically significant ($p \leq 0.05$).

Statistically significant differences were observed between the febuxostat 240 mg QD group and each of the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD groups in the incidence of diarrhea (excluding infective) (13% versus 6%, 7%, and 6%, respectively), between the febuxostat 240 mg QD and each of the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD groups in the incidence of neurological signs and symptoms not elsewhere classified (NEC) (7% versus 2%, 2%, and 2%, respectively). Also, statistically significant differences were noted between the allopurinol 300/100 mg QD group and each of the placebo and febuxostat 80 mg QD groups in the incidence of vascular hypertensive disorders NEC (1% versus 6% and 5%, respectively) and between the placebo group and each of the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD groups in the incidence of muscle related signs and symptoms NEC (5% versus 1%, <1%, and <1%, respectively).

Overall, the incidence of treatment-related adverse events was 21% in the febuxostat 80 mg QD group, 18% in the febuxostat 120 mg QD group, 16% in the allopurinol 300/100 mg QD group, 29% in the febuxostat 240 mg QD group and 23% in the placebo group.

3.2.1.2 Study # C02-010

Summary of patients with most frequent adverse event during treatment is given in Table 19 in the appendix. Of the 760 randomized subjects who received study drug 205 (80%) subjects in the febuxostat 80 mg QD group, 189 (75%) subjects in the febuxostat 120 mg QD group, and 215 (85%)

subjects in the allopurinol 300 mg QD group reported at least one adverse event during treatment. The difference between the febuxostat 120 mg QD and allopurinol 300 mg QD groups for the overall incidence of treatment-emergent adverse events was statistically significant ($p \leq 0.05$).

3.2.1.3 Study # TMXTMX-00-004

Summary of patients with most frequent adverse event during treatment is given in Table 20 in the appendix. The number of subjects who experienced adverse events was similar among the placebo and the febuxostat treatment groups (50% placebo, 54% febuxostat 40 mg QD, 58% febuxostat 80 mg QD and 50% febuxostat 120 mg QD). There were no statistically significant differences between each febuxostat treatment group and placebo in the overall incidence of adverse events or in the incidence of any specific treatment-emergent or study drug-related adverse event. However, diarrhea was observed more frequently in the febuxostat 80 mg QD treatment group (20%) compared to the placebo, febuxostat 40 mg QD and febuxostat 120 mg QD treatment groups (11%, 3% and 11%, respectively). The majority of the adverse events reported were mild or moderate in severity.

At least one adverse event was reported by 50% (19/38) of the placebo group, 54% (20/37) of the febuxostat 40 mg QD group, 58% (23/40) of the febuxostat 80 mg QD and 50% (19/38) of the febuxostat 120 mg QD group. Three subjects (1 febuxostat 80 mg QD and 2 febuxostat 120 mg QD) reported serious adverse events. No subjects died during the study.

3.2.1.4 Study # C02-021

Safety data from the start of the study up to and including 30 April 2004 are contained in the clinical database and are included in this interim analysis. In addition, SAE data from the Pharmacovigilance database from 1 May 2004 to 9 July 2004 are included for further safety information. A total of 1074 subjects received at least one dose of study drug and are included in this interim analysis.

The most frequently reported adverse events, based on MedDRA HLT, are shown in Table 21 in the appendix. Overall, 39% (283/731) of subjects who received febuxostat 80 mg QD, 27% (110/405) of subjects who received febuxostat 120 mg QD, and 26% (42/162) of subjects who received allopurinol 300/ 100 mg QD reported at least one treatment-emergent adverse event. The most common treatment-emergent adverse events were upper respiratory tract infection, joint related disorders, lower respiratory tract and lung infection, influenza viral infection, headache, diarrhea, musculoskeletal and connective tissue signs and symptoms, and paresthesias and dysesthesias.

3.2.2 REVIEWER'S ANALYSIS OF SAFETY DATA

This reviewer did not perform any analysis on the safety data. This reviewer refers to the clinical review for safety analysis.

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4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 SPONSOR'S SUB-GROUP ANALYSIS

Under the 'Sub-Group Analysis' heading, the sponsor presented the analysis of efficacy variables after statistically adjusting the sub-group categories (CMH). Such results show the drug effects in the overall population after adjusting for the possible differences in the sub-group categories. However,

in an appropriate sub-group analysis we want to see the efficacy results in each sub-group separately. In this sense the sponsor's sub-group analysis is not quite relevant. However, analysis results after such adjustment of subgroup categories may be of interest from some other points of view. Keeping this in mind, this reviewer presents brief summaries of sponsor's analysis in the following.

4.1.1 STUDY #C 02-009

The sponsor analyzed the proportion of subjects whose last 3 serum urate levels were <6.0 mg/dL using the CMH by adjusting for gender (male, female), age (<45, 45 to <65, ≥65), race (Caucasian, non-Caucasian), overall compliance (<80%, 80 to <90%, ≥90%), baseline serum creatinine (≤1.5 mg/dL, >1.5 mg/dL), baseline measured 24-hour creatinine clearance (<50 mL/min/1.73 m2, ≥50 mL/min/1.73 m2), baseline serum urate level (<9.0, 9.0 to <10.0, ≥10.0 mg/dL), baseline palpable tophus presence (present, absent), previous use of urate-lowering therapy (prior use, no prior use), history of cardiovascular risk factors (≥1 risk factor, no risk factor [including history of cardiovascular disease, diabetes, hypercholesterolemia, hyperlipidemia, or hypertension]), alcohol use (non-/ex-drinker, drinker), baseline BMI (<18.5, 18.5 to <25, 25 to <30, ≥30 kg/m2), use of low-dose aspirin (yes, no), tobacco use (non-/ex-tobacco user, tobacco user), and metabolic syndrome (yes, no [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]).

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.

4.1.2 STUDY #C 02-010

Similar to Study #C 02-009 the sponsor also analyses the proportion of subjects in this study whose last 3 serum urate levels were <6.0 mg/dL by adjusting for gender (male, female), age (<45, 45-<65, ≥65), race (Caucasian, non-Caucasian), overall compliance (<80%, 80-<90%, ≥90%), baseline renal function (normal, impaired), baseline serum urate level (<9.0, 9.0-<10.0, ≥10.0 mg/dL), baseline palpable tophus presence (present, absent), previous use of urate-lowering therapy (prior use, no prior use), history of renal calculi, history of cardiovascular risk factors (≥1 risk factor, no risk factor [including history of cardiovascular disease, diabetes, hypercholesterolemia, hyperlipidemia, or hypertension]), alcohol use (non-/ex-drinker, drinker), baseline BMI (<18.5, 18.5-<25, 25-<30, ≥30 kg/m2), use of low-dose aspirin (yes, no), baseline calculated creatinine clearance using ideal body weight (<50, 50-<80, 80-<120, ≥120 mL/min), tobacco use (non-/ex-tobacco user, tobacco user), and metabolic syndrome (yes, no [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]).

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.

4.1.3 STUDY #TMX-TMX-00-004

Success rates were summarized for the following subject subgroups of interest: by subjects' baseline serum urate levels (≤9.0, >9.0-10.0, >10.0 mg/dL), gender (male, female) and renal function (normal, impaired), baseline urine uric acid production (underexcretor, overproducer) and baseline tophus presence (tophus present, tophus absent). Subjects with creatinine clearance levels of ≤80 mL/min on Day 1 were classified as having renal impairment. Subjects with a Day 1 urine uric acid level of ≤800 mg/day were classified as underexcretors while those with a Day 1 urine uric acid level of >800 mg/day were classified as overproducers. The percent reduction in serum urate levels from baseline to Day 28 was also summarized by baseline creatinine levels (<1.0 mg/dL, 1.0-1.5 mg/dL, >1.5 mg/dL), baseline urine uric acid production and baseline tophus presence.

Results of the success rates summarized by subgroups were generally similar to the overall analysis, regardless of which serum urate evaluation method (enzymatic or HPLC) was used. In addition, 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.

4.1.4 STUDY #C02-021

No sub-group analysis was performed.

4.2 REVIEWER'S SUB-GROUP ANALYSIS

This reviewer performed subgroup analysis of the primary efficacy variable by gender, age, and race using the 28 weeks data for Study #C02-009 and 52 weeks data for Study #C02-010. Tables 22 and 23 show this reviewer's results for Studies #C02-009 and #C02-010, respectively. Most of the sub-groups with moderate sample size showed statistically significant effects of both dose groups of febuxostat compared to allopurinol and placebo.

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5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

In this submission the sponsor included reports of two double-blind Phase 3 studies namely, Study #C02-009 and Study #C02-010, and one Phase 2 study namely, Study #C TMX-00-004. The sponsor also submitted report of an open-label safety extension of Studies #C02-009 and #C02-010 under Study #C02-021. At the time of this submission Study #C02-021 was ongoing. Results from an interim analysis of this study were submitted. The objectives of these studies were to compare the safety and efficacy of some selected doses of febuxostat to allopurinol and placebo for ⎯⎯⎯ ⎯ subjects with gout.

b(4)

Since Study #C TMX-00-004 was an inadequately powered short term Phase 2 study and Study #C02-021 was an incomplete open label safety extension study, this reviewer's efficacy conclusion of

the study drug was primarily based on Studies #C02-009 and #C02-010. However, results from the other two studies were also considered.

The primary efficacy variable was the proportion of responders, defined as having the last three observed uric acid level less than 6.0 mg/dL. Results from Study #C02-009 showed statistically significant difference in efficacy of all three study doses (80, 120 and 240 mg QD) of febuxostat compared to placebo. Results from this study also showed statistically superior efficacy of febuxostat 80 mg QD compare to 300 mg of allopurinol by a superiority margin of 13% and by more than 13% for other doses. Twenty eight weeks data from Study #C02-010 showed statistically superior efficacy of febuxostat 80 mg QD by a superiority margin of 24% and by 34% for febuxostat 120 mg QD. Fifty two weeks data from the same study showed statistically superior efficacy of febuxostat 80 mg QD by a superiority margin of 23% and by 35% for febuxostat 120 mg QD. Results from Studies #C TMX-00-004 and #C02-021 also showed favorable efficacy for febuxostat.

5.2 CONCLUSIONS AND RECOMMENDATIONS

Since the length of Study #C02-009 was 28 weeks and that of Study #C02-010 was 52 weeks, for appropriate overall conclusion this reviewer considered data up to 28 weeks from each study. Based on the results from Studies #C02-009 and #C02-010 and also taking the outcomes of Studies #C TMX-00-004 and #C02-021 into account, this reviewer concludes that overall all doses of febuxostat showed statistically significant difference in efficacy compared to placebo. Results from both studies also demonstrated a superior efficacy of febuxostat 80 mg QD and 120 mg QED after 28 week by a superiority margin of 13%, and by more than 13% for other doses.

In this study the reduction of serum urate was considered as a surrogate to the reduction of gout flares. The treatment with all study doses of febuxostat showed highly statistically significant efficacy with respect to the reduction of serum urate. However, results from the secondary efficacy endpoints showed that the percentages of subjects requiring treatment for gout flare in febuxostat groups were not statistically significantly different from that of placebo or allopurinol group. The following table shows the percentages of subjects requiring treatment for gout flares in Studies #C 02-009 and #C 02-010, also percentage of subjects with incidence of gout flare in Study #TMX-00-004.

| | Placebo | Febuxostat | | | | Allopurinol |
		40 mg	80 mg	120 mg	240 mg	
Study #C 02-009	55%		57%	62%	66%	51%
Study #C 02-010				64%	72%	65%
Study # TMX-00-004	37%	35%				

Therefore, the strength of correlation of this surrogate variable to the reduction of gout flare can be questioned. A clinical judgment is required in this respect.

This reviewer did not perform any analysis on the safety data. This reviewer refers to the clinical review for safety analysis.

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Mathematical Statistician

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HFD-715/ Dr. Permutt
HFD-725/ Dr. Rahman
HFD-700/Dr. Anello

**APPEARS THIS WAY
ON ORIGINAL**

6 APPENDIX

Table 1
Disposition of Patients
Study # C 02-009

	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)a						
<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						
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%)

Source: Table 10.1a

Table 2
Demographic and Baseline Characteristics
ITT Population
Study #C 02-009

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 (%)
Gender						
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%)
Race						
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%)
Age (years)a						
<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
Weight (pounds)						
N	134	267	268	134	267	1070
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
Height (inches)a						
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
BMI (kg/m2)a						
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
Menopausal History (females)						
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%)
Tobacco Use						
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%)
Alcohol Use						
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%)

Source: Table 11.2a of sponsor's analysis

Table 3
Proportion of Subjects with Last Three Serum Urate Levels < 6.0 mg/dL
Using All Available Data (Sensitivity Analysis) - ITT Subjects
Study #C 02-009

	Placebo	Febuxostat 80 mg QD	Febuxostat 120 mg QD	Febuxostat 240 mg QD	Allopurinol 300/100 mg QD
Last 3 Serum Urate < 6.0 mg/dL &					
Yes	0.0% (0/127)	56.5% (143/253)	70.2% (186/265)	82.5% (104/126)	24.7% (65/263)
No	100.0% (127/127)	43.5% (110/253)	29.8% (79/265)	17.5% (22/126)	75.3% (198/263)

		Difference in Proportions	97.5% CI (a)	P-values (b)	
		---------------	---------------	------------	
Primary Comparisons					
Febux 80 mg vs Allo 300/100 mg		31.8%	(22.6%, 41.0%)	<0.001‡	
Febux 120 mg vs Allo 300/100 mg		45.5%	(36.8%, 54.1%)	<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				0.001***	
Febux 80 mg vs Febux 240 mg				<0.001***	
Febux 120 mg vs Febux 240 mg				0.010**	

& For subjects who prematurely terminated before at least three serum urate levels were obtained, response was determined using the available (one or two) serum urate levels. Subjects without post-baseline serum urate levels are excluded from this analysis.
(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.

Source: Table 14.2.1.2 of sponsor's analysis

Table 4
Proportion of Subjects Whose Last 3 Serum Urate Levels were
<6.0 mg/dL by Baseline Serum Creatinine Levels - ITT Subjects
Study #C 02-009

Baseline Serum Creatinine Level	Placebo		Febuxostat 80 mg QD[p,m,h]		Febuxostat 120 mg QD[p,a]		Febuxostat 240 mg QD[p,a]		Allopurinol 300/100 mg QD[p]	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
≤1.5 mg/dL	0/129	(0%)	123/253	(48%)	170/258	(66%)	89/129	(69%)	60/253	(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

Source: Table 11.4b of sponsor's analysis

Table 5
Proportion of Subjects Whose Last 3 Serum Urate Levels were <6.0 mg/dL by Baseline Serum Urate - ITT Subjects
Study #C 02-009

Baseline Serum Urate Level	Placebo		Febuxostat 80 mg QD[p,a,m,h]		Febuxostat 120 mg QD[h,a]		Febuxostat 240 mg QD[p,a]		Allopurinol 300/100 mg QD[p]	
	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

Source: Table 11.4c of sponsor's analysis

Table 6
Disposition of Patients
Study #C 02-010

	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)[a]				
<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[a]:				
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

Source: Table 10.1a of sponsor's analysis

Table 7
Demographic Data at Baseline - All Subjects
Study #C 02-010

Variable	Febuxostat 80 mg QD (N=256)	Febuxostat 120 mg QD (N=251)	Allopurinol 300 mg QD (N=253)	All Subjects (N=760)
Gender				
Female	13 (5%)	8 (3%)	10 (4%)	31 (4%)
Male	243 (95%)	243 (97%)	243 (96%)	729 (96%)
Race				
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%)
Age (years)[a]				
<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
Weight (pounds)[a]				
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
Height (inches)[a]				
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
BMI (kg/m²)[a]				
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
Menopausal History (females)				
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%)
Tobacco Use				
Non-/Ex-Tobacco User	213 (83%)	208 (83%)	208 (82%)	629 (83%)
Tobacco User	43 (17%)	43 (17%)	45 (18%)	131 (17%)
Alcohol Use				
Non-/Ex-Drinker	85 (33%)	93 (37%)	80 (32%)	258 (34%)
Drinker	171 (67%)	158 (63%)	173 (68%)	502 (66%)

a   At baseline
Statistical Table 14.1.3.1 and Appendices 16.2-4.1, 16.2-4.3, and 16.2-4.5

Source: Table 11.2a of sponsor's analysis

Table 8
Proportion of Subjects Whose Last 3 Serum Urate Levels were
<6.0 mg/dL at Week 28 - ITT Subjects
Study #C 02-010

Last 3 Serum Urate Levels <6.0 mg/dL	Febuxostat 80 mg QD n/N (%)		Febuxostat 120 mg QD n/N (%)		Allopurinol 300 mg QD n/N (%)	
Yes	132/255	(52%)[†]	163/250	(65%)	50/251	(20%)
No	123/255	(48%)	87/250	(35%)	201/251	(80%)

	Difference in Proportions	97.5% CI[a]	P-value[b]
Febuxostat 80 mg vs. Allopurinol	32%	(22.8%, 40.9%)	<0.001[&]
Febuxostat 120 mg vs. Allopurinol	45%	(36.5%, 54.1%)	<0.001[&]

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

Source: Table 11.4b of sponsor's analysis

Table 9
Proportion of Subjects Whose Last 3 Serum Urate Levels were
<6.0 mg/dL by Baseline Serum Urate Level - ITT Subjects
Study #C 02-010

Baseline Serum Urate Level	Febuxostat 80 mg QD[a] n/N (%)		Febuxostat 120 mg QD[a] n/N (%)		Allopurinol 300 mg QD 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

Source: Table 11.4c of sponsor's analysis

Table 10
Disposition of Subjects
Study # TMX-00-004

	Treatment Group			
	Placebo	Feburostat 40 mg QD	Feburostat 80 mg QD	Feburostat 120 mg QD
All Randomized Subjects	38	37	40	38
Completed Study	36	36	37	36
Prematurely Terminated	2	1	3	2
Primary Reason:				
Adverse Event	1	1	2	2
Gout Flare	1	0	0	0
Other	0	0	1ᵃ	0

a   Subject non-compliant with study drug dosing.
Cross Reference: Statistical Table 14.1.2 and Appendix 16.2-1.1

Source: Table 10.1a of sponsor's analysis

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Table 11
Demographic Data at Baseline
Study # TMX-00-004

Variable	Placebo (N=38)	Febuxostat 40 mg QD (N=37)	Febuxostat 80 mg QD (N=40)	Febuxostat 120 mg QD (N=38)
Gender				
Male	32 (84%)	33 (89%)	38 (95%)	33 (87%)
Female	6 (16%)	4 (11%)	2 (5%)	5 (13%)
Race				
Caucasian	32 (84%)	32 (87%)	35 (88%)	34 (89%)
Black	3 (8%)	3 (8%)	3 (8%)	2 (5%)
Hispanic	1 (3%)	1 (3%)	1 (3%)	1 (3%)
Asian	0 (0%)	0 (0%)	1 (3%)	1 (3%)
Other	2 (5%)	1 (3%)	0 (0%)	0 (0%)
Age				
<45	12 (32%)	8 (22%)	10 (25%)	7 (18%)
45-<65	17 (45%)	21 (57%)	19 (48%)	23 (61%)
≥65	9 (24%)	8 (22%)	11 (28%)	8 (21%)
Mean (SD)	52.4 (12.63)	52.2 (14.04)	55.2 (13.09)	56.2 (10.83)
Range	33-76	23-80	29-78	34-76
Weight (lb)[a]				
Mean (SD)	221.3 (33.75)	219.8 (32.19)	236.9 (51.89)	218.0 (46.18)
Range	165-322	170-279	158-377	137-350
Height (in)[a]	(N=38)	(N=37)	(N=40)	(N=37)
Mean (SD)	69.5 (2.63)	69.8 (3.68)	70.6 (2.72)	69.7 (3.59)
Range	63-76	62-80	66-76	60-75
BMI (kg/m²)[a]	(N=38)	(N=37)	(N=40)	(N=37)
≤25	0 (0%)	2 (5%)	3 (8%)	3 (8%)
>25-≤30	13 (34%)	12 (32%)	12 (30%)	14 (37%)
>30-≤35	16 (42%)	16 (43%)	12 (30%)	12 (32%)
>35-≤40	6 (16%)	4 (11%)	7 (18%)	5 (13%)
>40	3 (8%)	3 (8%)	6 (15%)	3 (8%)
Missing	0 (0%)	0 (0%)	0 (0%)	1 (3%)
Mean (SD)	32.2 (4.82)	31.8 (4.55)	33.2 (6.58)	31.6 (6.12)
Range	26-48	24-42	23-50	24-46
Urine Uric Acid[b]				
Underexcretor	30 (79%)	29 (78%)	29 (73%)	30 (79%)
Overproducer	8 (21%)	8 (22%)	9 (23%)	7 (18%)
Missing	0 (0%)	0 (0%)	2 (5%)	1 (3%)
Palpable Tophus[c]				
Yes	9 (24%)	6 (16%)	10 (25%)	11 (29%)
No	29 (76%)	31 (84%)	30 (75%)	27 (71%)

a At baseline

b Based on 24-hour urine collection at baseline. Underexcretor: uric acid ≤800 mg/day; overproducer: uric acid >800 mg/day.

c Presence of a palpable tophus at baseline.

Cross Reference: Statistical Table 14.1.3 and Appendices 16.2-4.1, 16.2-6.1.5 and 16.2-6.3.

Source: Table 11.2a of sponsor's analysis

Table 12
Disposition of Patients
Study #C02-021

	All Subjects n	Treatment Receiving at Time of Discontinuation		
		Febuxostat 80 mg QD n	Febuxostat 120 mg QD n	Allopurinol 300/100 mg QD n
Number Enrolled[a]	1074			
Number Ongoing[b]	1013 (94%)			
Number Prematurely Discontinued	61 (6%)			
Timing of Premature Discontinuation				
≤1 Month	20	12	6	2
>1 to 3 Months	26	16	6	4
>3 to 6 Months	11	6	5	0
>6 Months	4	0	4	0
Primary Reason for Premature Discontinuation				
Adverse Event	12	8	4	0
Protocol Violation	2	2	0	0
Personal Reason(s)	10	7	3	0
Lost to Follow-up	13	7	4	2
Therapeutic Failure	3	0	3	0
Gout Flare	3	1	2	0
Other	18	9	5	4

a   Subjects in the database who have taken study drug on or before 30 April 2004
b   Subjects still in the study as of 30 April 2004, the date of the cut-off for the interim analysis
Cross-reference: Statistical Table 14.1.1

Source: Table 10.1a

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Table 13
Demographic and Baseline Characteristics by Initial Treatment
Assignment for Study C02-021
Study #C 02-021

Variable	Febuxostat 80 mg QD N=650 n (%)	Febuxostat 120 mg QD N=282 n (%)	Allopurinol 300/100 mg QD N=142 N (%)
Gender			
Male	626 (96)	267 (95)	138 (97)
Female	24 (4)	15 (5)	4 (3)
Race			
Asian	18 (3)	2 (1)	5 (4)
Black	51 (8)	30 (11)	15 (11)
Caucasian	521 (80)	226 (80)	108 (76)
Hispanic	40 (6)	14 (5)	10 (7)
Other	20 (3)	10 (4)	4 (3)
Age (years)[a]			
<28	10 (2)	2 (1)	0
28-37	70 (11)	40 (14)	19 (13)
38-45	128 (20)	45 (16)	30 (21)
46-55	213 (33)	90 (32)	40 (28)
>55	229 (35)	105 (37)	53 (37)
Mean	51.4	51.1	51.1
SD	11.94	11.60	11.37
Range	24-84	24-84	29-83
Weight (pounds)[a]			
Mean	233.4	231.5	233.8
SD	42.97	47.38	49.62
Range	123-390	142-399	136-468
Renal Function[a]			
Normal	637 (98)	276 (98)	141 (99)
Impaired: serum creatinine >1.5 mg/dL	13 (2)	6 (2)	1 (1)

a The baseline demographic values are the last observations obtained prior to receiving the first
   dose of study drug in either Study C02-009 or Study C02-010.
Cross-reference: Statistical Table 14.1.2 and Appendix 16.2.4.1

Source: Table 11.2a of sponsor's analysis

Table 14
Initial Treatment Assignment in Study C02-021 By Prior
Treatment Assignment in Study C02-009 or C02-010

Prior Treatment Assignment[a]	Initial Treatment Assignment		
	Febuxostat 80 mg QD N=650 n (%)	Febuxostat 120 mg QD N=282 n (%)	Allopurinol 300/100 mg QD N=142 n (%)
Febuxostat 80 mg QD	176 (27)	69 (24)	37 (26)
Febuxostat 120 mg QD	184 (28)	79 (28)	36 (25)
Febuxostat 240 mg QD	34 (5)	25 (9)	12 (8)
Allopurinol 300/100 mg QD	209 (32)	85 (30)	46 (32)
Placebo	47 (7)	24 (9)	11 (8)

a Treatment taken in the previous Study C02-009 or Study C02-010
Cross-reference: Statistical Table 14.1.2, and Appendices 16.2.5.2.1, 16.2.5.2.2

Source: Table 10.2b of sponsor's analysis

Table 15
Number of Subjects Initially Assigned to and Receiving at least one Dose of Each Treatment
Study #C02-021

Number of Subjects	Febuxostat 80 mg QD N	Febuxostat 120 mg QD N	Allopurinol 300/100 mg QD N
Initially assigned	650	282	142
Who took at least 1 dose[a]	731	405	162

a Subjects may be included in more than 1 treatment.
Cross-reference: Statistical Table 14.1.3 and Appendices 16.2.5.2.1, 16.2.5.2.2

Source: Table 11.2C of sponsor's analysis

Table 16
Summary of First Treatment Change for Subjects Enrolled after Protocol Amendment #2
Study #C02-021

	Initial Treatment		
	Febuxostat 80 mg QD N=299	Febuxostat 120 mg QD N=278	Allopurinol 300/100 mg QD N=142
First Treatment Change	n (%)	n (%)	n (%)
Overall	36 (12)	47 (17)	49 (35)
Febuxostat 80 mg QD	-	33 (12)	48 (34)
Febuxostat 120 mg QD	33 (11)	-	1 (<1)
Allopurinol 300/100 mg QD	3 (1)	14 (5)	-

Cross-reference: Statistical Table 14.1.5 and Appendices 16.2.5.2.1, 16.2.5.2.2

Source: Table 11.2d of sponsor's analysis

Table 17

Summary of Reasons for Treatment Change for Subjects Who Enrolled after Protocol Amendment #2
Study #C02-021

Reason for Treatment Change	Febuxostat 80 mg QD N=299			Febuxostat 120 mg QD N=278			Allopurinol 300/100 mg QD N=142		
	n (%)	Changed to: F120	Allo	n (%)	Changed to: F80	Allo	n (%)	Changed to: F80	F120
Serum Urate >6.0 mg/dL	24 (8)	24	0	13 (5)	0	13	44 (31)	43	1
Serum Urate <3.0 mg/dL	0	0	0	20 (7)	20	0	0	0	0
Adverse Event	2 (1)	0	2	2 (1)	2	0	1 (1)	1	0
Other	5 (2)	4	1	8 (3)	7	1	2 (1)	2	0
Unspecified	5 (2)	5	0	4 (1)	4	0	2 (1)	2	0

F80 = febuxostat 80 mg QD; F120 = febuxostat 120 mg QD; Allo = allopurinol 300/100 mg QD
Cross-reference: Statistical Table 14.1.5 and Appendices 16.2.5.2.1, 16.2.5.2.2

Source: Table 11.2e of sponsor's analysis

Table 18
Most Frequent MedDRA High Level Terms Observed during the
28-Week Double-Blind Treatment Period
Study #C 02-009

MedDRA High Level Term Preferred Term	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)
Total Subjects with at Least 1 Adverse Event	97 (72%)	181 (68%)	183 (68%)	98 (73%)	200 (75%)
Upper Respiratory Tract Infections Laryngitis, Nasopharyngitis, Pharyngitis, Rhinitis, Sinusitis, Upper Respiratory Tract Infection	21 (16%)	39 (15%)	52 (19%)	27 (20%)	52 (19%)
Musculoskeletal & Connective Tissue Signs & Symptoms NEC Back Pain, Chest Wall Pain, Flank Pain, Muscle Spasms, Musculoskeletal Pain, Musculoskeletal Stiffness, Neck Pain, Nodule on Extremity, Pain in Extremity	23 (10%)	23 (9%)	24 (9%)	14 (10%)	27 (10%)
Diarrhoea (Excluding Infective) Diarrhoea	11 (8%)	16 (6%)ᵖ	19 (7%)ᵖ	18 (13%)ᵃ	17 (6%)
Joint Related Signs & Symptoms Arthralgia, Joint Effusion, Joint Stiffness, Joint Swelling	7 (5%)	17 (6%)	23 (9%)	7 (5%)	20 (7%)
Headaches NEC Headache, Sinus Headache	7 (5%)	14 (5%)	14 (5%)	12 (9%)	19 (7%)
Liver Function Analyses Alanine Aminotransferase Increased, Aspartate Aminotransferase Increased, Blood Bilirubin Increased, Hepatic Enzyme Increased, Liver Function Test Abnormal, Transaminases Increased	3 (2%)	17 (6%)	10 (4%)	6 (4%)	15 (6%)
Influenza Viral Infections Influenza	6 (4%)	11 (4%)	13 (5%)	7 (5%)	10 (4%)
Nausea & Vomiting Symptoms Nausea, Vomiting	5 (4%)	12 (4%)	10 (4%)	8 (6%)	5 (2%)
Non-site Specific Injuries NEC Arthropod Bite, Arthropod Sting, Contusion, Excoriation, Fall, Injury, Laceration, Road Traffic Accident, Soft Tissue Injury, Wound	3 (2%)	11 (4%)	9 (3%)	9 (7%)	8 (3%)
Vascular Hypertensive Disorders NEC Hypertension	8 (6%)	15 (5%)ᵃ	6 (2%)	6 (4%)	3 (1%)ᵖ
Gastrointestinal & Abdominal Pains (Excluding Oral & Throat) Abdominal Pain, Abdominal Pain Lower, Abdominal Pain Upper, Abdominal Tenderness	3 (2%)	6 (2%)	7 (3%)	8 (6%)	6 (2%)

NEC = not elsewhere classified

Note: Most frequent was defined as those high level terms reported by ≥5% of subjects in any treatment group.

ᵖ Statistically significant difference versus placebo (p≤0.05) using Fisher's exact test
ᵃ Statistically significant difference versus allopurinol 300/100 mg QD (p≤0.05) using Fisher's exact test
ʰ Statistically significant difference versus febuxostat 240 mg QD (p≤0.05) using Fisher's exact test

Statistical Tables 14.3.1.1 and 14.3.1.7 and Appendix 16.2-7.1

Source: Table 12.2a of sponsor's analysis

Table 18 (Continued)
Most Frequent MedDRA High Level Terms Observed during the
28-Week Double-Blind Treatment Period
Study #C 02-009

MedDRA High Level Term Preferred Term	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)
Neurological Signs & Symptoms NEC Dizziness, Dysravria	2 (1%)	5 (2%)²	5 (2%)²	9 (7%)²	5 (2%)
Muscle Related Signs & Symptoms NEC Muscle Cramp, Muscle Twitching, Night Cramps	7 (5%)	3 (1%)²	2 (<1%)²	2 (1%)	1 (<1%)²

NEC = not elsewhere classified
Note: Most frequent was defined as those high level terms reported by ≥5% of subjects in any treatment group.
²   Statistically significant difference versus placebo (p≤0.05) using Fisher's exact test.
ª   Statistically significant difference versus allopurinol 300/100 mg QD (p≤0.05) using Fisher's exact test.
ᵇ   Statistically significant difference versus febuxostat 240 mg QD (p≤0.05) using Fisher's exact test.
Statistical Tables 14.3.1.1 and 14.3.1.7 and Appendix 16.2-7.1
Source: Table 12.2a of sponsor's analysis

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Table 19

Most Frequent MedDRA High Level Terms Observed During the
52-Week Double-blind Treatment Period
Study #C 02-010

MedDRA High Level Term MedDRA Preferred Terms	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 Adverse Event	205 (80%)	189 (75%)[a]	215 (85%)
Upper Respiratory Tract Infections Acute Sinusitis, Acute Tonsillitis, Laryngitis, Nasopharyngitis, Pharyngitis, Rhinitis, Sinusitis, Upper Respiratory Tract Infection	77 (30%)[f]	53 (21%)	72 (28%)
Musculoskeletal & Connective Tissue Signs & Symptoms NEC Back Pain, Buttock Pain, Chest Wall Pain, Dupuytren's Contracture, Flank Pain, Muscle Spasms, Musculoskeletal Chest Pain, Musculoskeletal Discomfort, Musculoskeletal Stiffness, Neck Pain, Pain in Extremity	35 (14%)	38 (15%)	38 (15%)
Joint Related Signs & Symptoms Arthralgia, Joint Effusion, Joint Range of Motion Decreased, Joint Stiffness, Joint Swelling, Temporomandibular Joint Syndrome	39 (15%)	32 (13%)	37 (15%)
Diarrhoea (Excl Infective) Diarrhoea	27 (11%)	25 (10%)	16 (6%)
Headaches NEC Cluster Headache, Headache, Sinus Headache, Tension Headache	23 (9%)	23 (9%)	22 (9%)
Liver Function Analyses Alanine Aminotransferase Increased, Aspartate Aminotransferase Increased, Blood Bilirubin Increased, Hepatic Enzyme Increased, Liver Function Test Abnormal	13 (5%)	16 (6%)	12 (5%)
Nausea & Vomiting Symptoms Nausea, Vomiting	19 (7%)[a]	13 (5%)	8 (3%)
Upper Respiratory Tract Signs & Symptoms Hoarseness, Nasal Discomfort, Pharyngolaryngeal Pain, Postnasal Drip, Rhinorrhoea, Sinus Pain, Sneezing, Throat Irritation, Upper Respiratory Tract Congestion	13 (5%)	10 (4%)	17 (7%)
Influenza Viral Infections Influenza	12 (5%)	13 (5%)	12 (5%)
Non-Site Specific Injuries NEC Arthropod Bite, Arthropod Sting, Contusion, Excoriation, Fall, Injury, Laceration, Road Traffic Accident, Soft Tissue Injury, Wound	12 (5%)	10 (4%)	12 (5%)
Oedema NEC Oedema, Oedema Peripheral	18 (7%)	8 (3%)	8 (3%)
Limb Injuries NEC (Incl Traumatic Amputation) Cartilage Injury, Joint Injury, Joint Sprain, Limb Injury, Meniscus Lesion	12 (5%)	10 (4%)	11 (4%)
Neurological Signs & Symptoms NEC Dizziness, Dysgeusia	17 (7%)	9 (4%)	7 (3%)
Vascular Hypertensive Disorders NEC Hypertension	7 (3%)	10 (4%)	14 (6%)
Lower Respiratory Tract & Lung Infections Bronchitis, Bronchitis Acute, Pneumonia	13 (5%)	8 (3%)	8 (3%)

NEC = not elsewhere classified
Note: Most frequent was defined as those high level terms reported by ≥5% of subjects in any treatment group.
a   Statistically significant difference versus allopurinol 300 mg QD (p≤0.05) using Fisher's exact test
f   Statistically significant difference versus febuxostat 120 mg QD (p≤0.05) using Fisher's exact test
Statistical Tables 14.3.1.1 and 14.3.1.3 and Appendix 16.2-7.1

Source: Table 12.2a of sponsor's analysis

Table 20
Most Frequent Adverse Events Observed During the Treatment Period
Study #TMX-00-004

COSTART Term	Placebo (N=38)	Febuxostat 40 mg QD (N=37)	Febuxostat 80 mg QD (N=40)	Febuxostat 120 mg QD (N=38)
Total Subjects with at Least 1 Adverse Event	19 (50%)	20 (54%)	23 (58%)	19 (50%)
Abdominal Pain	3 (8%)	1 (3%)	1 (3%)	2 (5%)
Accidental Injury	0 (0%)	0 (0%)	2 (5%)	1 (3%)
Arthralgia	0 (0%)	2 (5%)	1 (3%)	2 (5%)
Back Pain	1 (3%)	3 (8%)	2 (5%)	3 (8%)
Diarrhea	4 (11%)	1 (3%)	8 (20%)	4 (11%)
Dyspepsia	0 (0%)	1 (3%)	2 (5%)	0 (0%)
Flu Syndrome	2 (5%)	1 (3%)	0 (0%)	1 (3%)
Headache	1 (3%)	3 (8%)	2 (5%)	2 (5%)
Increased Appetite	0 (0%)	2 (5%)	0 (0%)	0 (0%)
Infection	2 (5%)	1 (3%)	0 (0%)	1 (3%)
Liver Function Tests Abnormal	1 (3%)	2 (5%)	1 (3%)	1 (3%)
Myalgia	2 (5%)	1 (3%)	1 (3%)	2 (5%)
Pain	4 (11%)	6 (16%)	3 (8%)	2 (5%)
Pharyngitis	2 (5%)	0 (0%)	1 (3%)	0 (0%)
Rash	0 (0%)	0 (0%)	1 (3%)	3 (8%)

a   Adverse events reported by at least 2 subjects in any treatment group.
Cross Reference: Statistical Table 14.3.1.1 and Appendix 16.2-7.1.

Source: Table 12.2b of sponsor's analysis

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Table 21
Most Frequently Reported (≥2%) Treatment-Emergent Adverse Events
Study #C 02-021

MedDRA High Level Term/Preferred Term	Febuxostat 80 mg QD N= 731 n (%)	Febuxostat 120 mg QD N=405 n (%)	Allopurinol 300/100 mg QD N=162 n (%)
Total Subjects with at Least 1 Adverse Event	283 (39%)	110 (27%)	42 (26%)
Upper Respiratory Tract Infections	78 (11)	24 (6)	13 (8)
Nasopharyngitis	18 (2)	5 (1)	5 (3)
Pharyngitis	1 (<1)	0	0
Rhinitis	2 (<1)	0	0
Sinusitis	11 (2)	7 (2)	2 (1)
Tonsillitis	1 (<1)	0	0
Upper Respiratory Tract Infection	47 (6)	12 (3)	8 (5)
Joint Related Disorders NEC	25 (3)	8 (2)	2 (<1)
Arthralgia	19 (3)	6 (1)	1 (<1)
Joint effusion	2 (<1)	0	0
Joint stiffness	0	2 (<1)	1 (<1)
Joint swelling	4 (<1)	0	0
Lower Respiratory Tract and Lung Infections	17 (2)	5 (1)	0
Bronchiectasis	0	1 (<1)	0
Bronchitis	9 (1)	4 (<1)	0
Bronchitis acute	2 (<1)	0	0
Bronchitis chronic	1 (<1)	0	0
Lower respiratory tract infection	0	1 (<1)	0
Pneumonia	5 (<1)	1 (<1)	0
Influenza Viral Infections	16 (2)	5 (1)	1 (<1)
Influenza	16 (2)	5 (1)	1 (<1)
Headache NEC	16 (2)	9 (2)	1 (<1)
Headache	14 (2)	8 (2)	1 (<1)
Sinus headache	2 (<1)	2 (<1)	0
Diarrhoea	14 (2)	9 (2)	1 (<1)
Diarrhoea	14 (2)	9 (2)	1 (<1)
Musculoskeletal and Connective Tissue Signs and Symptoms NEC	14 (2)	8 (2)	4 (2)
Back pain	9 (1)	5 (1)	1 (<1)
Limb discomfort	0	0	1 (<1)
Muscle spasms	1 (<1)	1 (<1)	0
Neck pain	0	1 (<1)	1 (<1)
Pain in extremity	4 (<1)	2 (<1)	2 (<1)
Paraesthesias and Dysaesthesias	12 (2)	3 (<1)	0
Hypoaesthesia	7 (<1)	1 (<1)	0
Paraesthesia	5 (<1)	2 (<1)	0

NEC= not otherwise classified
All adverse events summarized were reported after first dose of study drug and no more than 30 days
after last dose of study drug. Subjects with 1 or more adverse events within a level of MedDRA term
are counted only once in that level. Subjects who received more than 1 treatment are counted in each
treatment, but adverse events are only summarized under the treatment most recently taken.
Cross-reference: Statistical Table 14.3.1.3

Source: Table 12.2.2a of sponsor's analysis

Table 22
Summary of Responders
(Last 3 Serum Uric acid Label <6)
Observations up to Week 28
NDA 21-856 Study # C 02-009
By Subgroup
Reviewer's Table

Subgroup	Treatment	N	Responder	Percent	P-value
All	FEBUXOSTAT 240 MG QD	134	87	65	<0.0001
	FEBUXOSTAT 120 MG QD	269	170	63	<0.0001
	FEBUXOSTAT 80 MG QD	267	121	45	<0.0001
	ALLOPURINOL 300/100 MG QD	268	61	24	
	PLACEBO	134	0	0	
FEMALE	FEBUXOSTAT 240 MG QD	8	5	63	0.3981
	FEBUXOSTAT 120 MG QD	13	10	77	0.0359
	FEBUXOSTAT 80 MG QD	16	11	69	0.0922
	ALLOPURINOL 300/100 MG QD	19	7	41	
	PLACEBO	11	0	0	
MALE	FEBUXOSTAT 240 MG QD	126	82	65	<0.0001
	FEBUXOSTAT 120 MG QD	256	160	63	<0.0001
	FEBUXOSTAT 80 MG QD	251	110	44	<0.0001
	ALLOPURINOL 300/100 MG QD	249	54	22	
	PLACEBO	123	0	0	
ASIAN	FEBUXOSTAT 240 MG QD	1	0	0	1.0000
	FEBUXOSTAT 120 MG QD	8	4	50	0.3007
	FEBUXOSTAT 80 MG QD	8	3	38	0.5804
	ALLOPURINOL 300/100 MG QD	6	1	17	
	PLACEBO	3	0	0	
BLACK	FEBUXOSTAT 240 MG QD	13	7	54	0.0924
	FEBUXOSTAT 120 MG QD	27	11	41	0.2703
	FEBUXOSTAT 80 MG QD	38	14	37	0.4375
	ALLOPURINOL 300/100 MG QD	33	8	26	
	PLACEBO	9	0	0	
CAUCASIAN	FEBUXOSTAT 240 MG QD	107	73	68	<0.0001
	FEBUXOSTAT 120 MG QD	214	143	67	<0.0001
	FEBUXOSTAT 80 MG QD	200	97	49	<0.0001
	ALLOPURINOL 300/100 MG QD	206	46	23	
	PLACEBO	108	0	0	
HISPANIC	FEBUXOSTAT 240 MG QD	8	5	63	0.1936
	FEBUXOSTAT 120 MG QD	16	10	63	0.0844
	FEBUXOSTAT 80 MG QD	13	4	31	1.0000
	ALLOPURINOL 300/100 MG QD	17	5	31	
	PLACEBO	10	0	0	

Table 22 (Continued)
Summary of Responders
(Last 3 Serum Uric acid Label <6)
Observations up to Week 28
NDA 21-856 Study # C 02-009
By Subgroup
Reviewer's Table

Subgroup	Treatment	N	Responder	Percent	P-value
OTHER	FEBUXOSTAT 240 MG QD	5	2	40	0.5455
	FEBUXOSTAT 120 MG QD	4	2	50	0.5000
	FEBUXOSTAT 80 MG QD	8	3	38	0.5804
	ALLOPURINOL 300/100 MG QD	6	1	20	
	PLACEBO	4	0	0	
45<=Age<65	FEBUXOSTAT 240 MG QD	71	46	65	<0.0001
	FEBUXOSTAT 120 MG QD	154	106	69	<0.0001
	FEBUXOSTAT 80 MG QD	146	74	51	<0.0001
	ALLOPURINOL 300/100 MG QD	147	36	25	
	PLACEBO	79	0	0	
Age<45	FEBUXOSTAT 240 MG QD	33	20	61	<0.0001
	FEBUXOSTAT 120 MG QD	79	39	49	<0.0001
	FEBUXOSTAT 80 MG QD	82	23	28	0.0097
	ALLOPURINOL 300/100 MG QD	82	9	11	
	PLACEBO	36	0	0	
Age>=65	FEBUXOSTAT 240 MG QD	30	21	70	0.0278
	FEBUXOSTAT 120 MG QD	36	25	69	0.0201
	FEBUXOSTAT 80 MG QD	39	24	62	0.1123
	ALLOPURINOL 300/100 MG QD	39	16	44	
	PLACEBO	19	0	0	

APPEARS THIS WAY
ON ORIGINAL

Table 23
Summary of Responders
(Last 3 Serum Uric acid Label <6)
Observations up to Week 52
NDA 21-856 Study # C 02-010
By Subgroup
Reviewer's Table

Subgroup	Treatment	N	Responder	Percent	P-value
All	FEBUXOSTAT 120 MG QD	251	139	55	<0.0001
	FEBUXOSTAT 80 MG QD	256	131	51	<0.0001
	ALLOPURINOL 300 MG QD	253	50	20	
FEMALE	FEBUXOSTAT 120 MG QD	8	4	50	1.0000
	FEBUXOSTAT 80 MG QD	13	8	62	0.4136
	ALLOPURINOL 300 MG QD	10	4	40	
MALE	FEBUXOSTAT 120 MG QD	243	135	56	<0.0001
	FEBUXOSTAT 80 MG QD	243	123	51	<0.0001
	ALLOPURINOL 300 MG QD	243	46	19	
ASIAN	FEBUXOSTAT 120 MG QD	9	5	56	0.0440
	FEBUXOSTAT 80 MG QD	10	7	70	0.0114
	ALLOPURINOL 300 MG QD	6	0	0	
BLACK	FEBUXOSTAT 120 MG QD	20	7	35	0.7342
	FEBUXOSTAT 80 MG QD	24	9	38	0.7417
	ALLOPURINOL 300 MG QD	18	5	28	
CAUCASIAN	FEBUXOSTAT 120 MG QD	199	120	60	<0.0001
	FEBUXOSTAT 80 MG QD	193	104	54	<0.0001
	ALLOPURINOL 300 MG QD	195	43	22	
HISPANIC	FEBUXOSTAT 120 MG QD	17	6	35	0.1138
	FEBUXOSTAT 80 MG QD	22	5	23	0.4192
	ALLOPURINOL 300 MG QD	19	2	11	
OTHER	FEBUXOSTAT 120 MG QD	6	1	17	0.2857
	FEBUXOSTAT 80 MG QD	7	6	86	0.0001
	ALLOPURINOL 300 MG QD	15	0	0	
45<Age<65	FEBUXOSTAT 120 MG QD	133	74	56	<0.0001
	FEBUXOSTAT 80 MG QD	140	76	54	<0.0001
	ALLOPURINOL 300 MG QD	125	26	21	
Age<45	FEBUXOSTAT 120 MG QD	71	34	48	<0.0001
	FEBUXOSTAT 80 MG QD	75	23	31	<0.0001
	ALLOPURINOL 300 MG QD	84	3	4	
Age>=65	FEBUXOSTAT 120 MG QD	47	31	66	0.0931
	FEBUXOSTAT 80 MG QD	41	32	78	0.0068
	ALLOPURINOL 300 MG QD	44	21	48	

/s/

Atiar Rahman
9/29/2005 10:02:05 AM
BIOMETRICS

Thomas Permutt
10/3/2005 09:05:59 AM
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S. Edward Nevius
10/12/2005 11:00:20 AM
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Concur with review.