No clinically relevant differences were observed across treatment groups in any demographic or baseline characteristic in the Phase 3 controlled studies. However, a lower mean weight was observed in the placebo group (215.2 pounds) compared to the febuxostat 80 mg QD, febuxostat 120 mg QD, febuxostat 240 mg QD, and allopurinol 300/100 mg QD treatment groups (226.2, 227.2, 227.2, and 224.4 pounds, respectively).

Table 53 (Sponsor's Table 2.4b, ISS)
Demographic Profile of Subjects in Controlled Trials
(Phase 3 Controlled Studies)

		Febuxostat				Allopurinol
Variable	Placebo (N=134)	All Doses (N=1177)	80 mg QD (N=523)	120 mg QD (N=520)	240 mg QD (N=134)	300/100 mg QD (N=521)
Gender						
Female	11 (8%)	58 (5%)	29 (6%)	21 (4%)	8 (6%)	29 (6%)
Male	123 (92%)	1119 (95%)	494 (94%)	499 (96%)	126 (94%)	492 (94%)
Race						
Caucasian	108 (81%)	913 (78%)	393 (75%)	413 (79%)	107 (80%)	401 (77%)
Black	9 (7%)	122 (10%)	62 (12%)	47 (9%)	13 (10%)	51 (10%)
Hispanic	10 (7%)	76 (6%)	35 (7%)	33 (6%)	8 (6%)	36 (7%)
Asian	3 (2%)	36 (3%)	18 (3%)	17 (3%)	1 (1%)	12 (2%)
Other	4 (3%)	30 (3%)	15 (3%)	10 (2%)	5 (4%)	21 (4%)
Age (years)[a]						
<45	36 (27%)	340 (29%)	157 (30%)	150 (29%)	33 (25%)	166 (32%)
45 to 65	82 (61%)	677 (58%)	297 (57%)	303 (58%)	77 (57%)	282 (54%)
>65	16 (12%)	160 (14%)	69 (13%)	67 (13%)	24 (18%)	73 (14%)
Mean (SD)	51.5 (12.18)	51.7 (12.04)	51.2 (11.98)	51.6 (11.83)	54.3 (12.83)	51.7 (12.42)
Range	26-82	22-84	22-84	23-81	30-82	24-84
Weight (pounds)[a]						
Mean (SD)	215.2 (43.05)	226.7 (45.77)	226.2 (45.87)	227.2 (46.84)	227.2 (49.04)	224.4 (44.02)
Range	123-360	133-468	133-396	136-468	139-425	136-447
Height (inches)[a]						
N	134	1176	523	519	134	567
Mean (SD)	69.1 (3.93)	69.7 (3.20)	69.7 (3.21)	69.8 (3.15)	69.7 (3.38)	69.6 (3.37)
Range	57-75	59-83	60-80	59-80	61-83	59-78
BMI (kg/m^2)[a]						
N	134	1176	523	519	134	567
<18.5	0	0	0	0	0	0
18.5 to <25	16 (12%)	57 (5%)	25 (5%)	23 (4%)	9 (7%)	22 (4%)
25 to <30	48 (36%)	370 (31%)	160 (31%)	168 (32%)	42 (31%)	180 (35%)
≥30	70 (52%)	749 (64%)	338 (65%)	328 (63%)	83 (62%)	315 (60%)
Mean (SD)	31.8 (6.32)	32.8 (6.10)	32.7 (5.93)	32.8 (6.16)	32.8 (6.55)	32.6 (5.95)
Range	21.8-53.2	20.3-64.6	20.3-60.2	20.7-63.5	21.0-64.6	19.6-64.1
Alcohol Use						
Non-/ Ex-Drinker	47 (35%)	417 (35%)	172 (33%)	190 (37%)	55 (41%)	157 (30%)
Drinker	87 (65%)	760 (65%)	351 (67%)	330 (63%)	79 (59%)	364 (70%)
Tobacco Use						
Non-/Ex-User	102 (76%)	953 (81%)	422 (81%)	421 (81%)	110 (82%)	430 (83%)
User	32 (24%)	224 (19%)	101 (19%)	99 (19%)	24 (18%)	91 (17%)

SD = standard deviation
Phase 3 studies included: C02-009 and C02-010 combined data.
a At baseline.
Cross-reference: Statistical Table 2.3.3

Among the 1177 febuxostat subjects enrolled in the Phase 3 controlled studies, 13% had a history of atherosclerotic disease, 46% had a history of hypertension, 2% had a history of congestive heart failure, 8% had a history of diabetes, 34% had a history of hyperlipidemia, 36% had a baseline calculated Cl_{cr} <80 mL/minute, 3% had a baseline serum creatinine value >1.5 mg/dL, 5% had a history of nephrolithiasis, 5% had a history of thyroid disease, and <1% had a history of peripheral neuropathy (**Table 54**).

Table 54 (Sponsor's Table 2.4c, ISS) Baseline Medical Conditions (Phase 3 Controlled Studies)

Variable	Placebo (N=134)	Febuxostat All Doses (N=1177)	Febuxostat 80 mg QD (N=523)	Febuxostat 120 mg QD (N=520)	Febuxostat 240 mg QD (N=134)	Allopurinol 300/100 mg QD (N=521)
Atherosclerotic Disease	18 (13%)	150 (13%)	61 (12%)	65 (13%)	24 (18%)	50 (10%)
Hypertension	61 (46%)	537 (46%)	230 (44%)	237 (46%)	70 (52%)	235 (45%)
Congestive Heart Failure	5 (4%)	27 (2%)	11 (2%)	10 (2%)	6 (4%)	8 (2%)
Diabetes	9 (7%)	94 (8%)	36 (7%)	46 (9%)	12 (9%)	40 (8%)
Hyperlipidemia	44 (33%)	398 (34%)	189 (36%)	169 (33%)	49 (37%)	162 (31%)
Calculated Creatinine Clearance <80 mL/minute[a,b]	45 (34%)	418 (36%)	183 (35%)	181 (35%)	51 (38%)	180 (35%)
Serum Creatinine >1.5 mg/dL[a]	3 (2%)	33 (3%)	11 (2%)	15 (3%)	7 (5%)	11 (2%)
Nephrolithiasis	3 (2%)	55 (5%)	26 (5%)	26 (5%)	3 (2%)	27 (5%)
Thyroid Disease	5 (4%)	55 (5%)	24 (5%)	18 (3%)	13 (10%)	27 (5%)
Peripheral Neuropathy	0	11 (<1%)	3 (<1%)	5 (<1%)	3 (2%)	1 (<1%)

Phase 3 studies included: C02-009 and C02-010 combined data.
a At baseline.
b Based on IBW and serum creatinine value at baseline. N = 519 and 517 in the febuxostat 120 mg QD and allopurinol 300/100 mg QD treatment groups, respectively.
Cross-reference: Statistical Table 2.3.3

Reviewer's comments:

- *Allopurinol group has a slightly lower rate of atherosclerotic disease and hyperlipidemia compared to febuxostat groups however the difference is small and unlikely would have any impact on the outcomes*
- *Febuxostat 240 mg group has slightly higher rates of underlying diseases across most variables compared to allopurinol and other doses of febuxostat*

The mean number of years with gout ranged from 9.9 to 12.2 years across all treatment groups (**Table 55**). Subjects with a history or presence of tophi ranged from 24-33% across all treatment groups.

Table 55 (Sponsor's Table 2.4d, ISS) Gout Disease History (Phase 3 Controlled Studies)

Variable	Placebo (N=134)	Febuxostat All Doses (N=1177)	Febuxostat 80 mg QD (N=523)	Febuxostat 120 mg QD (N=520)	Febuxostat 240 mg QD (N=134)	Allopurinol 300/100 mg QD (N=521)
History or Presence of a Tophus						
Yes	44 (33%)	303 (26%)	123 (24%)	144 (28%)	36 (27%)	138 (26%)
No	90 (67%)	874 (74%)	400 (76%)	376 (72%)	98 (73%)	383 (74%)
Years with Gout						
Mean (SD)	9.9 (8.13)	11.6 (9.35)	11.2 (9.36)	12.2 (9.50)	11.0 (8.66)	11.0 (9.16)
Range	<1-45	<1-63	<1-63	<1-63	<1-42	<1-51

Phase 3 studies included: C02-009 and C02-010 combined data.
Cross-reference: Statistical Table 2.3.3

The proportion of subjects who had a baseline serum urate level ≥10.0 mg/dL was 41%, 38%, and 37% in the febuxostat combined group, allopurinol 300/100 mg QD group, and placebo group, respectively (**Table 56**). Across all treatment groups, more than 30% of the subjects had a baseline serum urate level between 9.0 and <10.0 mg/dL. Nine subjects had a baseline serum urate level <8.0 mg/dL.

Table 56 (Sponsor's Table 2.4e, ISS) Baseline Serum Urate Level (Phase 3 Controlled Studies)

Baseline Serum Urate (mg/dL)	Placebo (N=134)	Febuxostat All Doses (N=1177)	Febuxostat 80 mg QD (N=523)	Febuxostat 120 mg QD (N=520)	Febuxostat 240 mg QD (N=134)	Allopurinol 300/100 mg QD (N=521)
<9.0	34 (25%)	322 (27%)	141 (27%)	145 (28%)	36 (27%)	144 (28%)
9.0 to <10.0	51 (38%)	375 (32%)	166 (32%)	161 (31%)	48 (36%)	177 (34%)
10.0 to <11.0	26 (19%)	272 (23%)	126 (24%)	121 (23%)	25 (19%)	104 (20%)
11.0 to <12.0	13 (10%)	138 (12%)	57 (11%)	63 (12%)	18 (13%)	61 (12%)
≥12.0	10 (7%)	70 (6%)	33 (6%)	30 (6%)	7 (5%)	35 (7%)

Phase 3 studies included: C02-009 and C02-010 combined data.
Cross-reference: Statistical Table 2.3.3

Reviewer's comments:

- *In the Phase 2/3 studies, subjects exposed to each treatment (placebo, febuxostat 40 to 240 mg and allopurinol) were primarily male and Caucasian. The proportions of subjects in each treatment group by gender, race, age, and weight were similar.*
- *Overall, allopurinol, febuxostat 80 mg and 120 mg groups were balanced with regards to demographic conditions and baseline characteristics*

7.2.1.3 Extent of exposure (dose/duration)

In the United States clinical program, 2518 subjects received ≥1 dose of febuxostat. A total of 1629 subjects were exposed to febuxostat 80 mg QD across the Phase 1/2/3 studies, of whom 1180 had hyperuricemia and a history or presence of gout. A total of 1012 subjects were exposed to febuxostat 120 mg QD across the Phase 1/2/3 studies, of whom 876 had hyperuricemia and a history or presence of gout.

Among all febuxostat doses combined, the mean duration of dosing was 176.6 days. The mean duration of dosing in the febuxostat 80 mg QD and 120 mg QD groups was 155.7 days and 159.0 days, respectively.

In the Phase 3 controlled studies, the exposure to study drug was similar between the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups, but higher compared to the febuxostat 240 mg QD and placebo groups.

Table 57 (Sponsor's Table 2.3b, ISS)
Study Subject Drug Exposure by Mean Daily Dose and Duration of Exposure (Phase 1/2/3 Studies)

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ON ORIGINAL

Treatment Duration (days)	Placebo[a]	Febuxostat QD (mg)							Allopurinol QD (mg)		
		10 - 70[a,b]	80[a]	90 - 110[a]	120[a]	130 - 240[a]	250 - 300[a]	Total[c]	100[a]	300[a]	Total[c]
Total Number of Subjects	172	304	1629	10	1012	164	52	2518	18	614	629
Number of Subjects											
1 to <7 days	3	115	290	0	79	7	42	356	1	12	12
7 days to <1 month	45	176	256	10	153	40	10	598	2	29	31
1 to <3 months	16	3	268	0	204	22	0	278	5	96	96
3 to <6 months	9	0	285	0	180	12	0	292	1	69	71
6 to <9 months	101	2	239	0	181	83	0	358	0	200	209
9 to <12 months	0	0	61	0	62	0	0	203	0	38	38
12 to <15 months	0	0	88	0	110	0	0	122	0	165	165
15 to <18 months	0	0	37	0	30	0	0	109	0	7	7
18 to <24 months	0	0	56	0	1	0	0	133	0	0	0
24 to <36 months	0	8	49	0	12	0	0	71	0	0	0
Mean (SD)	133.4 (79.87)	32.0 (121.55)	155.7 (192.52)	13.0 (0.00)	159.0 (152.08)	122.5 (83.29)	4.5 (1.29)	176.6 (207.76)	123.4 (81.34)	215.1 (124.78)	213.5 (124.25)
Min - Max	1 - 210	1 - 785	1 - 931	13 - 13	1 - 891	1 - 212	1 - 7	1 - 936	4 - 205	1 - 506	1 - 506

SD = standard deviation
Phase 1 studies included: TMX-99-001, TMX-00-002, TMX-00-003, TMX-00-006, TMX-01-008, TMX-01-009, TMX-01-010, TMX-01-012, TMX-01-014, TMX-01-016, TMX-02-017, TMX-02-018, C02-005, C02-006, C02-013, C02-023, C02-033, C02-034, C02-036, C03-040, C03-044, C03-051, C03-057, and C03-059.
Phase 2/3 studies included: TMX-00-004, TMX-01-005, C02-009, C02-010, and C02-021.
a Subjects who received study drug for more than 1 dose group are counted in each of those dose groups.
b Included 10 mg BID and 30 mg BID doses in Studies TMX-00-003 and TMX-99-001, respectively.
c Total displays exposure regardless of dose, not necessarily the sum of the individual dose columns.
Cross-reference: Statistical Table 2.1.1

Cumulative study subject drug exposure in all febuxostat studies (Phase 1/2/3) combined is summarized in **Table 58**.

Table 58 (Sponsor's Table 2.3c, ISS) Cumulative Study Subject Drug Exposure (Phase 1/2/3 Studies)

Cumulative Exposure	Placebo[a]	Febuxostat QD (mg)							Allopurinol QD (mg)		
		10 - 70[a,b]	80[a]	90 - 110[a]	120[a]	130 - 240[a]	250 - 300[a]	Total[c]	100[a]	300[a]	Total[c]
Number of Subjects											
≥1 day	172	304	1629	10	1012	164	52	2518	18	614	629
≥7 days	169	189	1339	10	933	157	10	2162	17	602	617
≥1 month	126	13	1083	0	780	117	0	1564	15	573	586
≥3 months	110	10	815	0	576	95	0	1286	10	479	490
≥6 months	101	10	330	0	396	83	0	994	9	410	419
≥9 months	0	8	291	0	215	0	0	636	0	210	210
≥12 months	0	8	230	0	133	0	0	433	0	172	172
≥15 months	0	8	142	0	43	0	0	311	0	7	7
≥18 months	0	8	105	0	13	0	0	202	0	0	0
≥24 months	0	8	49	0	12	0	0	71	0	0	0
≥36 months	0	0	0	0	0	0	0	0	0	0	0

Phase 1 studies included: TMX-99-001, TMX-00-002, TMX-00-003, TMX-00-006, TMX-01-008, TMX-01-009, TMX-01-010, TMX-01-012, TMX-01-014, TMX-01-016, TMX-02-017, TMX-02-018, C02-005, C02-006, C02-013, C02-023, C02-033, C02-034, C02-036, C03-040, C03-044, C03-051, C03-057, and C03-059.
Phase 2/3 studies included: TMX-00-004, TMX-01-005, C02-009, C02-010, and C02-021.
a Subjects who received study drug for more than 1 dose group are counted in each of those dose groups.
b Included 10 mg BID and 30 mg BID doses in Studies TMX-00-003 and TMX-99-001, respectively.
c Total displays exposure regardless of dose, not necessarily the sum of the individual dose columns.
Cross-reference: Statistical Table 2.1.1

Duration of total exposure and exposure by mean daily dose and cumulative study subject drug exposure in the Phase 3 controlled studies are summarized in **Table 59**.

In the Phase 3 controlled studies, **523, 520 and 521** subjects received ≥1 dose of study drug in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg treatment groups, respectively, while 134 subjects received ≥1 dose of study drug in each of the placebo and

febuxostat 240 mg groups. The mean treatment duration was lower in the placebo and febuxostat 240 mg QD treatment groups (**163.3 and 147.2 days**, respectively) compared to the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups (**218.3, 213.9, and 234.0 days**, respectively). In the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups, **423, 423, and 452** subjects were exposed for ≥3 months, respectively, while **95 and 110 subjects** were exposed for this duration in the febuxostat 240 mg QD and placebo treatment groups, respectively. In the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups, **370, 376 and 418** subjects were exposed for ≥6 months, respectively, while **83 and 101** subjects were exposed for this duration in the febuxostat 240 mg QD and placebo treatment groups, respectively. In the febuxostat 80 mg QD, febuxostat 120 mg QD and allopurinol 300/100 mg QD treatment groups, **179, 160, and 193** subjects were exposed for ≥9 months, respectively, while no subjects were exposed for 9 months or more in the febuxostat 240 mg QD or placebo treatment groups. A total of **152, 135, and 171** subjects were exposed for ≥1 year in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD groups, respectively.

Table 59 (Sponsor's Table 2.3f, ISS) Study Subject Drug Exposure (Phase 3 Controlled Studies)

Treatment Duration (days)	Placebo	Febuxostat QD (mg)				Allopurinol QD (mg)
		80	120	240	Total	300/100
Number of Subjects						
Total	134	523	520	134	1177	521
1 to <7 days	2	10	10	4	24	8
7 days to <1 month	10	31	25	13	69	26
1 to <3 months	12	59	62	22	143	33
3 to <6 months	9	53	47	12	112	34
6 to <9 months	101	191	216	83	490	225
9 to <12 months	0	27	25	0	52	22
12 to <15 months	0	152	135	0	287	171
15 to <18 months	0	0	0	0	0	0
Mean (SD)	163.3 (64.14)	218.3 (119.60)	213.9 (115.37)	147.2 (71.61)	208.3 (115.27)	234.0 (113.82)
Min - Max	1-210	1-385	1-394	1-212	1-394	1-389
Cumulative Exposure						
≥1 day	134	523	520	134	1177	521
≥7 days	132	513	510	130	1153	513
≥1 month	122	482	485	117	1084	487
≥3 months	110	423	423	95	941	452
≥6 months	101	370	376	83	829	418
≥9 months	0	179	160	0	339	193
≥12 months	0	152	135	0	287	171

SD = standard deviation
Phase 3 studies included: C02-009 and C02-010 combined data.
Cross-reference: Statistical Table 2.1.4

Reviewer's comments:

- *The number of subjects exposed to each of febuxostat doses exceeds the exposure recommended by ICH guidelines to assess both the short- and long-term safety of febuxostat 80 mg QD and 120 mg QD.*
- *In the Phase 3 controlled studies, the exposure to study drug was similar between the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups, but higher compared to the febuxostat 240 mg QD and placebo groups.*

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No postmarketing data or literature reports were used in the assessment of safety.

7.2.2.1 Other studies

None

7.2.2.2 Postmarketing experience

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

7.2.2.3 Literature

Literature review was not performed for the safety portion of the review.

7.2.3 Adequacy of Overall Clinical Experience

The doses of febuxostat proposed for registration in this application are 80 mg or 120 mg to be taken once a day.

The extent of exposure in the febuxostat clinical development program is considered sufficient to assess both the short- and long-term safety of febuxostat and these numbers exceed the number of subjects exposed in clinical studies recommended by ICH guidelines.

In Phase 1/2/3 studies, 2518 subjects have been exposed to at least one dose of febuxostat. In Phase 2/3 studies, 994 subjects were exposed to febuxostat for > 6 months and 433 subjects were exposed for at least 12 months. For the 80 mg QD and the 120 mg QD doses, the dosing regimen proposed in this registration, the mean duration of exposure in Phase 2/3 was 213 days and 182 days respectively. In addition, a 240 mg dose of febuxostat was studied in a 6-month Phase 3 study to provide safety information at twice the maximum dose proposed for registration. A 300 mg dose of febuxostat was also evaluated in a Phase 1, multiple dose study conducted to evaluate the potential for QT prolongation.

Pivotal studies included with this submission were adequately designed, evaluated different doses of febuxostat and included placebo and an active control.

The population studied included various demographic subsets and people with various risk factors and seem to appropriately reflect the population of patients who have hyperuricemia associated with gout.

Drug interaction studies were conducted with the classes of drugs expected to be most commonly used in the gout population.

However, of note, significant number of people was lost to follow-up in this clinical program or discontinued form the study due to personal reason, or other reasons. This could have affected the overall safety evaluation depending on reasons for lost to follow-up. However, it is highly unlikely that it would have changed the overall conclusion about the safety profile of febuxostat 80 mg and 120 mg QD.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Please, see Pharmacology/Toxicology review by Asoke Mukherjee, Ph.D.
In summary, TMX-67 is a xanthine oxidase inhibitor. It is devoid of inhibitory activities in several enzymes involved in the DNA synthesis. TMX-67 was genotoxic in the chromosomal aberration assay. TMX-67 showed papilloma and carcinoma of transitional cell in the urinary bladder in rodents. The neoplastic changes were secondary to calculus formation in the kidney and urinary tract. It is not teratogenic and did not affect fertility and reproductive performance in rats. Major toxicity profile based on the non-clinical studies is increased xanthine deposition and formation of crystals in the kidney and urinary tract due to low solubility of xanthine (1 mg/15 ml of water).

Therefore, the proposed clinical dose of 120 mg daily (2 mg/kg) is safe from the organ system toxicity based on the non-clinical studies. However, the possibility of calculus formation in the kidney and urinary tract could not be ruled out as it was observed in rats, mice and dogs following chronic treatment at doses that had 3.0-16 folds human exposure based on AUC at MRHD.

It was concluded that TMX-67 (febuxostat) has no effect in the CNS, GI, cardiovascular and respiratory systems at pharmacodynamic doses. However, a transient hypotensive effect was observed in conscious beagle dogs at 5 and 50 mg/kg oral doses. TMX-67 showed a diuretic effect at 100 mg/kg single dose in rats associated with increased excretion of potassium, chloride and xanthine in the urine.

Asoke Mukherjee, Ph.D. recommendations are as follows: No new non-clinical studies are recommended.

7.2.5 Adequacy of Routine Clinical Testing

Throughout the US clinical program, the safety of febuxostat was assessed by adverse events, physical examinations, laboratory evaluations, vital signs, and electrocardiograms (ECGs). Rashes were monitored and documented on the case report form as well as a Rash Adverse Event Worksheet.

Routine clinical testing of study subjects appears adequate in this development program.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Please, see Section 5 of Dr. Schiffenbauer Review and the Clinical Pharmacology Review by Dr. Lei Zhang, Ph.D. E. Dennis Bashaw, Pharm.D. for details.

The conclusion from Clinical Pharmacology review:

1. The *in vivo* drug interaction potential of febuxostat with drugs that are xanthine oxidase (XO) substrates needs to be evaluated:

a. Theophylline: Febuxostat should be studied at its maximum proposed clinical dose and theophylline may be studied at a sub-therapeutic dose for decreasing side effects.
b. Mecaptopurine or azathioprine: Febuxostat should be studied at its maximum proposed clinical dose and mecaptopurine or azathioprine may be studied at a sub-therapeutic dose for decreasing side-effects.
The results of these studies will provide information on dose selection when these drugs are coadministered. Without such studies, febuxostat needs to be contraindicated with theophylline, mecaptopurine and azathioprine.

2. The induction potential of febuxostat on human CYP-P450 needs to be evaluaed. Such study could be conducted either *in vitro* (human hepatocytes) or *in vivo*. Based on the results to date, the sponsor may study induction potential on CYP3A and CYP1A first. If there is no induction on CYP3A, no further study to evaluate induction on CYP2C8 or CYP2C9 is needed. If there is induction on CYP3A, then they need to further study induction on CYP2C8 and CYP2C9.

3. We do not agree with the Sponsor's conclusions as they relate an absence of a drug-drug interaction with warfarin. The removal of subjects with an increased INR in the warfarin drugdrug interaction trial lowered the strength of the results. We also note that there are reports of increased INR values in the clinical database in subjects on febuxostat, b(4)

4. A review of the data presented in the NDA suggests that lower doses should be used in certain populations to maintain, on average, similar plasma levels with normal volunteers. In light of this should the 80 and 120mg doses be approved, b(5)

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Overall, there is an increased awareness about safety profile of marketed drugs, and cardiovascular safety in particular. No special safety studies to address this issue were performed. From this reviewer's point of view, the Sponsor conducted an adequate evaluation to detect possible adverse events with this new product which allowed to detect a potential safety

concern, cardiovascular safety in particular, with submitted database. Since submitted database showed an unacceptable cardio-vascular safety profile for both doses of febuxostat (80 and 120 mg) without clear dose-response effect, additional long-term studies to address safety of lower doses would be recommended.

b(5)

Additionally, a potential of febuxostat to prolong QT interval was adequately explored and no concerns were raised.

The evaluation of febuxostat potential for hepatotoxicity raised concern about such a potential, but no difference was observed between febuxostat and allopurinol with regard to hepatotoxicity. Again, most patients had multiple pre-existing conditions and were on multiple medications that are itself have known hepatotoxic potential therefore it is impossible to fully assess the extent of an association of hepatotoxicity with the study drug.

7.2.8 Assessment of Quality and Completeness of Data

Data provided with this application in this reviewer's opinion appear adequate and complete to allow the assessment of the safety profile of febuxostat.

The original Integrated Summary of Safety (ISS) included data from all completed clinical studies and interim analysis data from 2 ongoing studies. 120-day safety update collected safety data until 29 October 2004 for both ongoing Studies (TMX-01-005 and C02-021).

With regard to the data from the Japan development program, studies conducted in Japan by Teijin Pharma Limited (Teijin) were considered supportive for the original NDA. Therefore, limited information (deaths, SAEs, adverse events leading to premature discontinuation of study drug, and rash adverse events) from the Japan development program was included in the ISS and in the 4-month safety update.

7.2.9 Additional Submissions, Including Safety Update

Four-month safety update from ongoing studies was submitted and the results have been incorporated into the rest of the review.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The clinical development program for febuxostat in the United States was comprised of 24 PK Phase 1 studies, 2 Phase 2 studies, and 3 Phase 3 studies with the objective to demonstrate that febuxostat could safely and effectively manage hyperuricemia in patients with gout. Two of

these studies (1 Phase 2 and 1 Phase 3) are extension studies and are currently ongoing. The proposed marketed doses of febuxostat are 80 mg QD and 120 mg QD. In addition, the licensing partner for TAP, Teijin, conducted a clinical development program consisting of 15 clinical trials in Japan in a different patient population with doses lower than those developed in the United States (up to 40 mg).

In the United States clinical program, a total of 2518 subjects received at least 1 dose of febuxostat. Nine hundred ninety-four subjects were exposed to any dose of febuxostat for ≥6 months and 433 were exposed for 12 months. As for the febuxostat 80 mg QD dose, 1629 subjects were exposed to at least 1 dose and 530 and 230 subjects were exposed for ≥6 and ≥12 months, respectively. As for the febuxostat 120 mg QD dose, 1012 subjects received at least 1 dose and 396 and 153 were exposed for 6 and 12 months, respectively. The extent of exposure in the febuxostat clinical development program is considered sufficient to assess both the short- and long-term safety of febuxostat and these numbers exceed the number of subjects exposed in clinical studies recommended by ICH guidelines.

The assessment of the clinical safety of febuxostat was done primarily by evaluation of the pooled Phase 3 controlled studies (Studies C02-009 and C02-010). Allopurinol, the only marketed XO inhibitor, in doses of 300 or 100 mg QD (based on baseline renal function) was selected as an active comparator in both studies. A febuxostat dose of 240 mg QD was added to Study C02-009 to obtain safety data at double the highest expected marketed dose. Within the pooled Phase 3 data, exposure to febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD was similar, but the exposure to febuxostat 240 mg QD and placebo was lower due to the different designs of studies C02-009 and C02-010.

This safety review incorporates data from 120-day safety update. Safety data collected until 29 October 2004 for ongoing Studies TMX-01-005 and C02-021 were included in the update. Severe adverse events (SAEs) reported from 30 October 2004 to 31 December 2004 were included as well. Serious adverse events and premature discontinuations due to adverse events reported in Japan program were included in the ISS.

No clinically relevant differences were observed across treatment groups in any demographic or baseline characteristic in the Phase 2/3 studies. The demographics and the medical history of the study subjects enrolled in the febuxostat development program are considered to be similar to the general gout population.

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

Among allopurinol 300/100 mg QD subjects enrolled in the Phase 2/3 studies, the majority were male (95%) and most were Caucasian (76%). Subjects ranged in age from 24 to 84 years, with a

mean age of 51.5 years. The mean BMI for all allopurinol 300/100 mg QD subjects was 32.8 kg/m2 and 61% had a BMI of ≥30 kg/m2.

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

There were total of 8 deaths reported for subjects taking febuxostat (3 febuxostat 80 mg QD and 5 febuxostat 120 mg QD) including **two deaths due to a myocardial infarction.** No deaths were reported in the allopurinol 300/100 mg QD, febuxostat 240 mg QD, febuxostat 40 mg QD, or placebo treatment groups. Review of patients' narratives in most cases did not allow to exclude a possible causal association with the study drug with a possible exception of a death due to metastatic colon CA. Two rare cases of retroperitoneal hemorrhage resulted in deaths occurred in patients on febuxostat and warfarin. In addition to that, three more cases on increased INR were reported as SAE in patients on concomitant warfarin. Despite the Sponsor's formal study evaluating the PK/PD interaction of those two drugs and its conclusion that there was no interaction, this reviewer came to a different conclusion [redacted] b(4)

According to the Sponsor, the incidence of serious adverse events (SAE) in phase 2/3 studies was 5% in the febuxostat 80 mg QD, 5% in the febuxostat 120 mg QD, 5% in the allopurinol treatment group and 1 % in placebo group. The most frequently occurring serious adverse events in the febuxostat 80 mg QD and 120 mg QD treatment groups included the MedDRA preferred terms cardiac failure congestive, myocardial infarction, atrial fibrillation, and chest pain. The most frequently occurring serious adverse events in the allopurinol 300/100 mg QD treatment group included the MedDRA preferred terms coronary artery disease, diverticulitis, and osteoarthritis.

This reviewer would like to point out that when SAEs are presented by MedDRA preferred terms since the numbers under each term are small, there seems to be no difference between treatment groups. However, review of patients' narratives with SAEs and discontinuations from the study due to SAEs produced different results (Table 11 of the review), especially with regards to thromboembolic cardio-vascular AEs. The numbers are different from those appearing in Sponsor's statistical tables. One possible explanation to this is that not all cases were coded correctly. Here is an example:

Subject 4665
Age: 75
Race: Black
Gender: Male
Significant Medical History: diabetes mellitus, hypertension, and coronary artery bypass surgery
Social History: non-drinker; non-tobacco user
Concomitant Medications: glyburide, atenolol, terazosin hydrochloride, lisinopril, and citalopram

Study Drug History: Day -5 to Day -1: colchicine 0.6 mg QD
Day 1-35: febuxostat 120 mg QD/colchicine 0.6 mg QD
Day 36-59: febuxostat 120 mg QD
On Day 21, the subject was hospitalized for a severe hypoglycemic seizure (MedDRA PT: Hypoglycaemic Seizure) that led to premature discontinuation from the study on Day 60. The subject experienced a tonic-clonic seizure and was transported to the hospital where his blood glucose level was found to be 22 mg/dL (normal range not provided). The subject reported consuming alcohol at the time of the event and had not eaten a meal that day or the evening prior while continuing to take his oral hypoglycemic medications. He was treated with an ampule of D50 and D5 normal saline intravenous drip. His blood sugar subsequently increased to the low 100's. On routine evaluation, a CT scan of the head revealed a frontal lobe meningioma for which the subject was asymptomatic. The subject had a troponin level of 0.226 and creatine phosphokinase (CPK) level of 291 U/L (normal ranges not provided). An adenosine stress test was performed to evaluate these findings. Results of the stress test were consistent with an inferolateral to inferior infarct with surrounding peri-infarct ischemia. Per the hospital records, the elevated troponin level likely represented a troponin leak secondary to his dehydrated state and not an acute coronary syndrome. Lab results also revealed BUN of 56 mg/dL and creatinine of 2.7 mg/dL (normal ranges not provided). After rehydration, his creatinine level was 1.4 mg/dL. The subject recovered and the event resolved on Day 28. The investigator's causality assessment was not related to the study drug and an alternative etiology of diabetes was provided. **The investigator did not consider the findings of myocardial infarction, meningioma, and acute renal failure to be SAEs.**

This reviewer identified 12 myocardial infarctions (including two deaths) in febuxostat treatment groups and only one in allopurinol group. In addition to that there were 7 cases of CVA vs. 0 in allopurinol group. When those two events are combined as confirmed thromboembolic events, the difference is quite striking: **19 vs. 1 (one)**. In addition to that there were 7 cases of atrial fibrillation in febuxostat group vs 0 in allopurinol, 8 cases of CHF/CHF exacerbation in febuxostat groups vs. 1 in allopurinol group, 3 cases of renal failure/insufficiency in febuxostat groups vs 0 in allopurinol.

Though this reviewer has no plausible explanation for such a significant difference in the number of thromboembolic events between febuxostat and allopurinol treatment groups, it is highly unlikely that this happened by chance alone. This reviewer's causality assessment for the thromboembolic events is that causal association with febuxostat cannot be excluded. Of note, most of those patients had multiple pre-existing morbidities including cardio-vascular diseases and were on multiple medications as was the case for allopurinol cohort as well since all groups were balanced in terms of their background characteristics.

This reviewer did not observe dose-response however the numbers of events are relatively small and might not allow a dose-response determination.

Of note, SAE submitted from Japan clinical program seem to be of different nature and are less concerning than SAE observed in US clinical program. Different population and different doses could serve as the possible explanation to this observation.

Among subjects who participated in the United States Phase 2/3 febuxostat clinical program, 162 (127 of 1707 receiving febuxostat, 27 of 629 receiving allopurinol 300/100 mg QD, and 8 of 172 receiving placebo) prematurely discontinued from study drug at least in part due to 1 or more adverse events occurring after the first dose of study drug and within 30 days of a subject's final dose. In the Phase 2/3 studies, the incidence of premature discontinuations due to treatment-emergent adverse events was the highest in the febuxostat 120 mg QD (10%), followed by other doses of febuxostat, placebo (5%), and allopurinol 300/100 mg QD had the lowest rate of 4%. The United States Phase 2/3 clinical febuxostat program was conducted with NSAIDs or colchicine prophylaxis during the first 2-4 weeks (Phase 2) or 8 weeks (Phase 3) of the studies. Colchicine has known side effects, which include diarrhoea, nausea, and vomiting. Furthermore, subjects in the febuxostat 240 mg QD treatment group may have had increased use of these agents due to gout flares. Thus, the association between colchicine and the incidence of premature discontinuations was analyzed. When only those adverse events leading to premature discontinuation were counted while a subject was not taking colchicine, the overall incidence of premature discontinuations due to adverse events in the Phase 3 controlled studies was 4%, 6%, and 3% in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups, respectively, and 3% and 3% in the febuxostat 240 mg QD and placebo treatment groups, respectively The most common AE that led to discontinuation from the study drug was liver function abnormalities in febuxostat all doses combined, and those AEs were numerically higher than in allopurinol group. Renal function abnormalities were also more common in febuxostat group compared to allopurinol group.

There seems to be no difference in the incidence of premature discontinuations due to treatment-emergent adverse events between febuxostat 80 mg and 120 mg groups.

The overall incidence of treatment-emergent adverse events in the phase 2/3 studies was 60%, 57%, and 70% in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups, respectively, and 73%, 63%, and 67% in the febuxostat 240 mg QD, febuxostat 40 mg QD, and placebo treatment groups, respectively.
The 10 most commonly reported treatment-emergent adverse events during febuxostat 40-240 mg QD treatment included the following MedDRA preferred terms:
nasopharyngitis, upper respiratory tract infection, diarrhea, arthralgia, headache, pain in extremity, influenza, back pain, nausea, and hypertension.
The 11 most commonly reported treatment-emergent adverse events during allopurinol 300/100 mg QD treatment included the following MedDRA preferred terms: upper respiratory tract infection, arthralgia, nasopharyngitis, headache, diarrhea, pain in extremity, back pain, influenza, sinusitis, hypertension, and constipation.
Incidence of diarrhea, headaches NEC, neurological signs and symptoms NEC, gastrointestinal and abdominal pains, nausea and vomiting were highest in febuxostat 240 mg group. There was no difference in the incidence of adverse events (AEs) by MedDRA high level term between febuxostat 80 and 120 mg. There was a slightly higher incidence of nausea and vomiting in

febuxostat vs allopurinol groups (4% and 3 % vs 2%, respectively) and diarrhea. Incidence of upper respiratory infections (URI) and musculoskeletal and connective tissue symptoms are slightly higher in allopurinol group compared to either of febuxostat groups. Those differences were not considered clinically significant.

The Sponsor performed analyses of laboratory values over time, which focuses on mean change from baseline at Weeks 28 and 52 as well as individual subject changes. The analyses encompass both shift analyses and potentially concerning laboratory values analyses. None of the findings seem to present a serious concern.

Of note, noticeable shift to high PTT values in febuxostat groups, especially in 120 mg group may provide a clue to why there were several patients on coumadin whose INR value increased while on co-administered febuxostat.

Febuxostat 80 mg and 120 mg groups had the highest rates of increased ALT ≥2 (65/508, or 13% and 65/506, or 13% respectively) compared to allopurinol and placebo groups (49/506, or 10% and 8/129, or 6%, respectively). Fewer subjects had an ALT ≥5 x ULN or ALT ≥10 x ULN with or without concurrent increase in bilirubin ≥2 mg/dL. However, there was no difference between febuxostat and allopurinol groups and no dose effect was observed.

A higher incidence for shift to high for BUN was noted in all active treatment groups. In addition, as for potentially concerning high BUN, a higher incidence was noted in the febuxostat 120 mg and 240 mg QD groups. However, when the analysis of potentially concerning values was performed only in those subjects not taking NSAIDs/COX-2 inhibitors at the time of the laboratory assessment, a higher incidence of potentially concerning BUN was only observed in the febuxostat 240 mg QD group. This was not accompanied by a concurrent increase in shift to high in serum creatinine or a decrease in measured Cl_{cr}. Therefore, it appears that the higher incidence of potentially concerning BUN values in active treatment may be due to subjects taking NSAIDs.

Analysis of vital signs and ECGs did not raise significant concerns. No clinically meaningful differences between groups for the mean change from baseline and for potentially concerning diastolic and systolic blood pressure and heart rate results were noted. In addition, febuxostat in doses of up to 300 mg QD in healthy volunteers and in doses of up to 240 mg QD in patients with gout did not have an effect on cardiac repolarization.

Summarizing all of the above, it appears that there is an increased risk of thrombotic cardio-vascular adverse events associated with the use of febuxostat 80 mg and 120 mg compared to allopurinol. The doses proposed for marketing pose unacceptable risk therefore cannot be recommended for an approval.

Exploration of lower doses is recommended and establishing safety of lower doses of febuxostat would be crucial since no dose-effect was demonstrated with the current database.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The assessment of the clinical safety of febuxostat was done primarily by evaluation of the pooled Phase 3 controlled studies (Studies C02-009 and C02-010). Since both studies used similar doses of febuxostat, used allopurinol as an active comparator, and the population enrolled was similar, pooling data allowed for more precise estimation of the incidence of adverse events given the relatively small numbers of events. Since the placebo and febuxostat 240 mg QD treatment groups were only included in Study C02-009, statistical comparisons were performed only between and/or within the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups for the analyses of the Phase 3 controlled studies.

A febuxostat dose of 240 mg QD was added to Study C02-009 to obtain safety data at double the highest expected marketed dose. Within the pooled Phase 3 data, exposure to febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD was similar, but the exposure to febuxostat 240 mg QD and placebo was lower due to the different designs of studies C02-009 and C02-010.

7.4.1.2 Combining data

The integrated safety analyses were conducted for 3 main groupings of studies: Phase 1 studies, Phase 2/3 studies, and Phase 3 controlled studies (C02-009 and C02-010). Since the studies were similar in design and population, the pooling of data was simply performed by combining the numerator events and denominators for selected studies.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

In Phase 1, multiple-dose Study TMX-99-001, subjects received placebo or febuxostat 10, 20, 30, 40, 50, 70, 90, 120, 160, 180, 240 mg QD, or 30 mg BID for 13 days. The overall incidence of adverse events was 62% in the placebo group and ranged from 40% to 90% in the febuxostat groups. The sample size in each of the febuxostat treatment groups was 10, except for the 50 mg (n=20) and 40 mg (n=8) treatment groups. No dose-dependent increase in the overall incidence of adverse events was observed. The most common adverse event across groups was headache (range: 20% to 70%). The incidence of vasodilatation (flushing) was higher at the 160,

180, and 240 mg QD dose levels (50%, 40%, and 40%, respectively) compared to the lower dose levels (range: 0-25% for febuxostat 10-120 mg QD).

In Phase 2, dose-response Study TMX-00-004, the number of subjects who experienced adverse events was similar in the placebo, febuxostat 40 mg QD, febuxostat 80 mg QD, and febuxostat 120 mg QD treatment groups (50%, 54%, 58%, and 50%, respectively). **There was no consistent increase in the frequency with increasing dose for any adverse events.**

In Phase 3 Study C02-009, at least 1 treatment-emergent adverse event was reported by 68%, 68%, and 73% of subjects in the febuxostat 80 mg QD, febuxostat 120 mg QD, and febuxostat 240 mg QD treatment groups, respectively, compared with 72% and 75% of subjects in the placebo and allopurinol 300/100 mg QD treatment groups, respectively. Although the incidence of treatment-related adverse events was slightly higher in the febuxostat 240 mg QD treatment group (29%) compared to the febuxostat 80 mg QD and 120 mg QD treatment groups (21% and 18%, respectively), **no clear dose response was evident.**

Similar to the results of Study C02-009, results of the 52-week Phase 3 Study C02-010 demonstrated no increase in the incidence of adverse events with increasing dose. At least 1 treatment-emergent adverse event was reported by 80%, 75%, and 85% of subjects in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300 mg QD treatment groups, respectively. Similarly, the incidence of treatment-related adverse events was 25%, 24%, and 23% in the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300 mg QD treatment groups, respectively.

Conclusion: No dose-response was observed during treatment with febuxostat in doses of up to 240 mg QD.

7.4.2.2 Explorations for time dependency for adverse findings

For the Phase 3 controlled studies and for subjects with continuous exposure in Phase 2/3 studies, all adverse events and all treatment-related adverse events were summarized by MedDRA SOC, HLT, and preferred term by onset date relative to the first dose of study drug: 1 to <7 days, 7 days to <1 month, 1 to <3 months, 3 to <6 months, 6 to <9 months, 9 to <12 months, 12 to <15 months, 15 to <18 months, 18 to <24 months, and 24 to <36 months.

In the Phase 3 controlled studies, the time of adverse event onset in each of the febuxostat 80 mg QD and 120 mg QD treatment groups was generally comparable to that of the allopurinol 300/100 mg QD and placebo treatment groups. Generally, the incidence of adverse events was highest during the first 6 months of treatment, after which there was a general decline in the incidence of adverse events. **In general, no dose-related effects were noted for the onset of adverse events.**

A summary of the most frequent adverse events in the Phase 3 controlled studies is presented by time of onset in **Table 60.**

Table 60 (Sponsor's Table 3.7a)
Time of Onset of Most Frequent Adverse Events (Phase 3 Controlled Studies)

MedDRA High Level Term	Time Interval n (%)						
	1-<7 days	7 days-<1 month	1-<3 months	3-<6 months	6-<9 months	9-<12 months	12-<15 months
Treatment-Emergent Adverse Events							
Number of Subjects Treated							
Placebo	134	132	122	110	101		
Febuxostat 80 mg QD	523	513	482	423	370	179	152
Febuxostat 120 mg QD	520	510	485	423	376	160	135
Febuxostat 240 mg QD	134	130	117	95	83		
Allopurinol 300/100 mg QD	521	513	487	452	418	193	171
Total Subjects with at Least 1 Adverse Event							
Placebo	22 (16%)	30 (23%)	52 (43%)	47 (43%)	11 (11%)		
Febuxostat 80 mg QD	90 (17%)	144 (28%)	201 (42%)	188 (44%)	109 (27%)	75 (42%)	11 (7%)
Febuxostat 120 mg QD	66 (12%)	141 (28%)	188 (39%)	185 (44%)	87 (23%)	68 (43%)	6 (4%)
Febuxostat 240 mg QD	31 (23%)	31 (24%)	52 (44%)	43 (45%)	8 (10%)		
Allopurinol 300/100 mg QD	57 (11%)	145 (28%)	218 (45%)	222 (49%)	107 (26%)	79 (41%)	10 (6%)
Upper Respiratory Tract Infections							
Placebo	0	3 (2%)	8 (7%)	9 (8%)	3 (3%)		
Febuxostat 80 mg QD	4 (<1%)	29 (6%)	30 (6%)	40 (9%)	21 (6%)	16 (9%)	1 (<1%)
Febuxostat 120 mg QD	2 (<1%)	19 (4%)	31 (6%)	40 (9%)	10 (3%)	12 (8%)	0
Febuxostat 240 mg QD	2 (1%)	4 (3%)	6 (5%)	17 (18%)	2 (2%)		
Allopurinol 300/100 mg QD	2 (<1%)	20 (4%)	39 (8%)	50 (11%)	18 (4%)	17 (9%)	3 (2%)
Diarrhoea (Excl Infective)							
Placebo	4 (3%)	3 (2%)	3 (2%)	3 (3%)	0		
Febuxostat 80 mg QD	8 (2%)	11 (2%)	12 (2%)	10 (2%)	0	2 (1%)	1 (<1%)
Febuxostat 120 mg QD	13 (3%)	10 (2%)	12 (2%)	8 (2%)	2 (<1%)	3 (2%)	0
Febuxostat 240 mg QD	7 (5%)	3 (2%)	3 (3%)	5 (5%)	0		
Allopurinol 300/100 mg QD	11 (2%)	9 (2%)	7 (1%)	4 (<1%)	3 (<1%)	1 (<1%)	0

NEC = not elsewhere classified
Phase 3 studies included: C02-009 and C02-010 combined data.
Note: Study C02-009 was a 28-week trial that included placebo and febuxostat 240 mg QD treatment groups. Thus, data beyond the 6-<9 month interval are not applicable.
Most frequent treatment-emergent adverse events include only those high level terms that occurred in ≥5% of subjects in any treatment group and treatment-related adverse events include only those high level terms that occurred in ≥2% of subjects in any treatment group.
Cross-reference: Statistical Tables 3.14.1 and 3.15.1

MedDRA High Level Term	Time Interval n (%)						
	1-<7 days	7 days-<1 month	1-<3 months	3-<6 months	6-<9 months	9-<12 months	12-<15 months
Treatment-Emergent Adverse Events (continued)							
Musculoskeletal & Connective Tissue Signs & Symptoms NEC							
Placebo	1 (<1%)	4 (3%)	5 (4%)	7 (6%)	0		
Febuxostat 80 mg QD	3 (<1%)	9 (2%)	24 (5%)	17 (4%)	5 (1%)	7 (4%)	1 (<1%)
Febuxostat 120 mg QD	2 (<1%)	11 (2%)	21 (4%)	18 (4%)	14 (4%)	6 (4%)	1 (<1%)
Febuxostat 240 mg QD	0	5 (4%)	5 (4%)	4 (4%)	1 (1%)		
Allopurinol 300/100 mg QD	2 (<1%)	11 (2%)	23 (5%)	20 (4%)	9 (2%)	9 (5%)	1 (<1%)
Joint Related Signs & Symptoms							
Placebo	0	0	2 (2%)	5 (5%)	2 (2%)		
Febuxostat 80 mg QD	1 (<1%)	6 (1%)	20 (4%)	16 (4%)	9 (2%)	8 (4%)	2 (1%)
Febuxostat 120 mg QD	1 (<1%)	13 (3%)	20 (4%)	17 (4%)	14 (4%)	6 (4%)	0
Febuxostat 240 mg QD	0	3 (2%)	4 (3%)	1 (1%)	0		
Allopurinol 300/100 mg QD	7 (1%)	9 (2%)	15 (3%)	20 (4%)	9 (2%)	7 (4%)	2 (1%)
Headaches NEC							
Placebo	0	1 (<1%)	3 (2%)	3 (3%)	0		
Febuxostat 80 mg QD	7 (1%)	8 (2%)	13 (3%)	3 (<1%)	4 (1%)	4 (2%)	0
Febuxostat 120 mg QD	10 (2%)	5 (<1%)	11 (2%)	7 (2%)	4 (1%)	2 (1%)	0
Febuxostat 240 mg QD	4 (3%)	3 (2%)	5 (4%)	0	0		
Allopurinol 300/100 mg QD	8 (2%)	10 (2%)	18 (2%)	16 (4%)	4 (<1%)	1 (<1%)	0
Neurological Signs & Symptoms NEC							
Placebo	1 (<1%)	1 (<1%)	0	0	0		
Febuxostat 80 mg QD	3 (<1%)	2 (<1%)	4 (<1%)	9 (2%)	2 (<1%)	1 (<1%)	0
Febuxostat 120 mg QD	3 (<1%)	4 (<1%)	6 (1%)	0	1 (<1%)	0	0
Febuxostat 240 mg QD	2 (1%)	4 (3%)	4 (3%)	0	0		
Allopurinol 300/100 mg QD	2 (<1%)	2 (<1%)	2 (<1%)	3 (<1%)	2 (<1%)	1 (<1%)	0

MedDRA High Level Term	Time Interval n (%)						
	1-<7 days	7 days-<1 month	1-<3 months	3-<6 months	6-<9 months	9-<12 months	12-<15 months
Treatment-Emergent Adverse Events (continued)							
Non-Site Specific Injuries NEC							
Placebo	0	1 (<1%)	2 (2%)	0	0		
Febuxostat 80 mg QD	0	5 (<1%)	2 (<1%)	6 (1%)	9 (2%)	2 (1%)	0
Febuxostat 120 mg QD	1 (<1%)	2 (<1%)	5 (1%)	4 (<1%)	4 (1%)	3 (2%)	0
Febuxostat 240 mg QD	2 (1%)	1 (<1%)	4 (3%)	1 (1%)	0		
Allopurinol 300/100 mg QD	1 (<1%)	4 (<1%)	6 (1%)	8 (2%)	3 (<1%)	2 (1%)	0
Gastrointestinal & Abdominal Pains (Excl Oral & Throat)							
Placebo	1 (<1%)	0	3 (2%)	0	0		
Febuxostat 80 mg QD	3 (<1%)	3 (<1%)	5 (1%)	4 (<1%)	2 (<1%)	1 (<1%)	0
Febuxostat 120 mg QD	1 (<1%)	4 (<1%)	5 (1%)	2 (<1%)	0	1 (<1%)	0
Febuxostat 240 mg QD	1 (<1%)	5 (4%)	1 (<1%)	3 (3%)	0		
Allopurinol 300/100 mg QD	3 (<1%)	2 (<1%)	3 (<1%)	1 (<1%)	3 (<1%)	1 (<1%)	0
Nausea & Vomiting Symptoms							
Placebo	2 (1%)	2 (2%)	0	0	1 (<1%)		
Febuxostat 80 mg QD	5 (<1%)	3 (<1%)	10 (2%)	5 (1%)	1 (<1%)	4 (2%)	1 (<1%)
Febuxostat 120 mg QD	6 (1%)	7 (1%)	6 (1%)	3 (<1%)	1 (<1%)	1 (<1%)	0
Febuxostat 240 mg QD	2 (1%)	2 (2%)	3 (3%)	1 (1%)	0		
Allopurinol 300/100 mg QD	4 (<1%)	4 (<1%)	3 (<1%)	4 (<1%)	0	0	0
Vascular Hypertensive Disorders NEC							
Placebo	1 (<1%)	0	0	7 (6%)	1 (<1%)		
Febuxostat 80 mg QD	2 (<1%)	0	4 (<1%)	9 (2%)	3 (<1%)	1 (<1%)	0
Febuxostat 120 mg QD	3 (<1%)	5 (<1%)	2 (<1%)	3 (<1%)	0	2 (1%)	0
Febuxostat 240 mg QD	1 (<1%)	0	4 (3%)	1 (1%)	0		
Allopurinol 300/100 mg QD	1 (<1%)	3 (<1%)	0	6 (1%)	1 (<1%)	3 (2%)	0

MedDRA High Level Term	Time Interval n (%)						
	1-<7 days	7 days-<1 month	1-<3 months	3-<6 months	6-<9 months	9-<12 months	12-<15 months
Treatment-Emergent Adverse Events (continued)							
Liver Function Analyses							
Placebo	0	0	2 (2%)	1 (<1%)	0		
Febuxostat 80 mg QD	3 (<1%)	7 (1%)	8 (2%)	10 (2%)	4 (1%)	1 (<1%)	0
Febuxostat 120 mg QD	1 (<1%)	5 (<1%)	7 (1%)	9 (2%)	4 (1%)	2 (1%)	0
Febuxostat 240 mg QD	0	0	3 (3%)	2 (2%)	0		
Allopurinol 300/100 mg QD	1 (<1%)	8 (2%)	9 (2%)	6 (1%)	2 (<1%)	0	0
Influenza Viral Infections							
Placebo	0	0	2 (2%)	3 (3%)	1 (<1%)		
Febuxostat 80 mg QD	1 (<1%)	3 (<1%)	3 (<1%)	12 (3%)	4 (1%)	3 (2%)	0
Febuxostat 120 mg QD	0	3 (<1%)	8 (2%)	11 (3%)	1 (<1%)	2 (1%)	1 (<1%)
Febuxostat 240 mg QD	0	0	5 (4%)	2 (2%)	0		
Allopurinol 300/100 mg QD	0	2 (<1%)	7 (1%)	8 (2%)	2 (<1%)	3 (2%)	1 (<1%)
Muscle Related Signs & Symptoms NEC							
Placebo	0	2 (2%)	2 (2%)	3 (3%)	0		
Febuxostat 80 mg QD	0	0	1 (<1%)	2 (<1%)	0	3 (2%)	0
Febuxostat 120 mg QD	2 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)	0	0	0
Febuxostat 240 mg QD	2 (1%)	0	0	0	0		
Allopurinol 300/100 mg QD	0	2 (<1%)	1 (<1%)	1 (<1%)	0	0	0

MedDRA High Level Term	Time Interval n (%)						
	1-<7 days	7 days-<1 month	1-<3 months	3-<6 months	6-<9 months	9-<12 months	12-<15 months
Treatment-Related Adverse Events							
Total Subjects with at Least 1 Adverse Event							
Placebo	14 (10%)	9 (7%)	8 (7%)	2 (2%)	0		
Febuxostat 80 mg QD	40 (8%)	31 (6%)	42 (9%)	28 (6%)	9 (2%)	6 (3%)	0
Febuxostat 120 mg QD	28 (5%)	32 (6%)	29 (6%)	25 (6%)	12 (3%)	5 (3%)	0
Febuxostat 240 mg QD	17 (13%)	13 (10%)	14 (12%)	5 (5%)	1 (1%)		
Allopurinol 300/100 mg QD	25 (5%)	38 (7%)	27 (6%)	25 (6%)	10 (2%)	2 (1%)	0
Diarrhoea (Excl Infective)							
Placebo	3 (2%)	2 (2%)	1 (<1%)	0	0		
Febuxostat 80 mg QD	7 (1%)	4 (<1%)	4 (<1%)	0	0	1 (<1%)	0
Febuxostat 120 mg QD	7 (1%)	3 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)	0	0
Febuxostat 240 mg QD	4 (3%)	3 (2%)	2 (2%)	0	0		
Allopurinol 300/100 mg QD	6 (1%)	3 (<1%)	2 (<1%)	1 (<1%)	0	0	0
Headaches NEC							
Placebo	0	0	0	0	0		
Febuxostat 80 mg QD	2 (<1%)	1 (<1%)	3 (<1%)	0	0	0	0
Febuxostat 120 mg QD	5 (<1%)	3 (<1%)	1 (<1%)	4 (<1%)	0	0	0
Febuxostat 240 mg QD	3 (2%)	2 (2%)	1 (<1%)	0	0		
Allopurinol 300/100 mg QD	7 (1%)	3 (<1%)	1 (<1%)	2 (<1%)	0	0	0
Nausea & Vomiting Symptoms							
Placebo	1 (<1%)	0	0	0	0		
Febuxostat 80 mg QD	5 (<1%)	0	5 (1%)	0	0	1 (<1%)	0
Febuxostat 120 mg QD	3 (<1%)	1 (<1%)	0	1 (<1%)	1 (<1%)	0	0
Febuxostat 240 mg QD	2 (1%)	2 (2%)	3 (2%)	0	0		
Allopurinol 300/100 mg QD	2 (<1%)	2 (<1%)	0	1 (<1%)	0	0	0

MedDRA High Level Term	Time Interval n (%)						
	1-<7 days	7 days-<1 month	1-<3 months	3-<6 months	6-<9 months	9-<12 months	12-<15 months
Treatment-Related Adverse Events (continued)							
Neurological Signs & Symptoms NEC							
Placebo	1 (<1%)	0	0	0	0		
Febuxostat 80 mg QD	2 (<1%)	0	1 (<1%)	4 (<1%)	0	0	0
Febuxostat 120 mg QD	2 (<1%)	2 (<1%)	0	0	0	0	0
Febuxostat 240 mg QD	2 (1%)	3 (2%)	2 (2%)	0	0		
Allopurinol 300/100 mg QD	1 (<1%)	1 (<1%)	0	0	0	0	0
Gastrointestinal & Abdominal Pains (Excl Oral & Throat)							
Placebo	1 (<1%)	0	3 (2%)	0	0		
Febuxostat 80 mg QD	2 (<1%)	1 (<1%)	0	0	0	0	0
Febuxostat 120 mg QD	1 (<1%)	1 (<1%)	2 (<1%)	0	0	0	0
Febuxostat 240 mg QD	1 (<1%)	4 (3%)	0	1 (1%)	0		
Allopurinol 300/100 mg QD	1 (<1%)	1 (<1%)	0	0	1 (<1%)	0	0
Liver Function Analyses							
Placebo	0	0	1 (<1%)	0	0		
Febuxostat 80 mg QD	0	4 (<1%)	6 (1%)	6 (1%)	4 (1%)	1 (<1%)	0
Febuxostat 120 mg QD	1 (<1%)	2 (<1%)	4 (<1%)	6 (1%)	4 (1%)	2 (1%)	0
Febuxostat 240 mg QD	0	0	2 (2%)	1 (1%)	0		
Allopurinol 300/100 mg QD	1 (<1%)	6 (1%)	6 (1%)	5 (1%)	1 (<1%)	0	0
Peripheral Vascular Disorders NEC							
Placebo	0	0	1 (<1%)	0	0		
Febuxostat 80 mg QD	0	0	0	0	0	0	0
Febuxostat 120 mg QD	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	0	0	0
Febuxostat 240 mg QD	3 (2%)	0	0	0	0		
Allopurinol 300/100 mg QD	1 (<1%)	0	0	0	0	0	0

Reviewer's comments:

- *Overall incidence of AEs was increasing during the first 6 months on drug, and this increase was similar across treatment groups*
- *The incidence of diarrhea seems to be stable over time with the lowest incidence in allopurinol group and the highest in febuxostat 240 mg group*
- *Incidence of headache, neurological signs and symptoms, gastrointestinal/ and abdominal pain, vascular hypertensive disorders seems to be stable over time and similar across treatment groups*
- *Liver function tests abnormalities seem to increase during first 3-6 month of treatment, then slightly decline and this is similar across treatment groups*
- *Incidence of most treatment –related AEs as defined by the investigator seem to be stable over time and similar across treatment groups with the highest incidence of AEs in febuxostat 240 mg*

7.4.2.3 Explorations for drug-demographic interactions

Please, see Section 8.3

7.4.2.4 Explorations for drug-disease interactions

The disease factors in the drug-disease interaction analyses included renal insufficiency based on serum creatinine, renal insufficiency based on calculated Cl_{cr}, hepatic insufficiency, nephrolithiasis, thyroid disease, atherosclerotic disease, hypertension, congestive heart failure, diabetes, hyperlipidemia, and peripheral neuropathy. A subject was categorized as having renal insufficiency based on serum creatinine if he had a baseline value >1.5 mg/dL and based on calculated Cl_{cr} if he had a baseline value <80 mL/minute. Creatinine clearance was calculated at baseline based on the Cockroft-Gault equation using IBW, as suggested by Cockcroft and Gault when weight abnormalities are present in a study population. Ideal body weight was calculated as 50 kg for males and 45.5 kg for females plus 2.3 kg for each inch in height over 5 feet. Subjects were categorized as having the other disease factors based on a review of the medical history.

For all adverse events and all treatment-related adverse events, the numbers and percentages of subjects with adverse events with and without each disease were summarized by MedDRA SOC, HLT, and preferred term. Pairwise comparisons between the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups were performed using a Cochran-Mantel-Haenszel test adjusting for absence/presence of the disease. In addition, overall comparisons between subjects with and without each disease within each of the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups were performed using Fisher's exact test.

The numbers and percentages of subjects with potentially concerning laboratory values and elevated LFT values for subjects who had a medical history for each of the diseases were summarized. Pairwise comparisons between the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups were performed using Fisher's exact test. Summary statistics (N, mean, and SD) for the baseline, post-baseline, and change from baseline to post-baseline values were computed for all subjects who had a medical history for each of the disease factors for hematology, chemistry, endocrinology, and urinalysis variables. Summary statistics are presented only for those visits for which more than 5 subjects with a history of the specific disease factor had the specific laboratory test performed. If no visit for a given treatment group met this criteria, the treatment group was not presented on the summary table. Pairwise comparisons of the mean changes from baseline between the febuxostat 80 mg QD, febuxostat

120 mg QD, and allopurinol 300/100 mg QD treatment groups were made using contrast statements within the framework of an ANOVA model with treatment as the factor. Within each treatment group (including placebo and febuxostat 240 mg QD), the mean change from baseline to post-baseline values at each visit was tested versus zero using a one-sample paired t-test. In addition, the numbers and percentages of subjects with elevated liver function test (LFT) values were summarized by baseline ALT (within normal range, above normal range), baseline AST (within normal range, above normal range), and baseline calculated Cl_{cr} (<80, ≥80 mL/min) for the Phase 3 controlled studies.

7.4.2.5 Explorations for drug-drug interactions

See also Clinical Pharmacology review by Lei Zhang, Ph.D. and by Dennis Bashaw, Pharm.D.

The concomitant medications in the drug-drug interaction analyses included NSAIDs/COX-2 inhibitors, colchicine, aspirin, nitrates, ACE inhibitors, ®-blockers, HMG CoA reductase inhibitors, insulin, acetaminophen, corticosteroids, warfarin, thiazides, and calcium channel blockers.

All adverse events and all treatment-related adverse events that occurred while a subject was taking a given concomitant medication were summarized by MedDRA SOC, HLT, and preferred term. The numbers and percentages of subjects with potentially concerning laboratory values and elevated LFT values for subjects who took each of the concomitant medications were summarized. For adverse events, potentially concerning laboratory values, and elevated LFT values, Fisher's exact test was used to perform pairwise comparisons between the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups.

Summary statistics (N, mean, and SD) for the baseline, post-baseline, and change from baseline to post-baseline values were computed for subjects who took each of the concomitant medications for hematology, chemistry, endocrinology, and urinalysis variables. Summary statistics are presented only for those visits for which more than 5 subjects that took the given concomitant medication had the specific laboratory test performed. If no visit for a given treatment group met this criteria, the treatment group was not presented on the summary table. Pairwise comparisons of the mean changes from baseline between the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups were made using contrast statements within the framework of an ANOVA model with treatment as the factor. Within each treatment group (including placebo and febuxostat 240 mg QD), the mean change from baseline to post-baseline values at each visit was tested versus zero using a one-sample paired t-test.

Summaries of adverse events were generated for adverse events that occurred while subjects were taking theophylline, while subjects were taking either NSAIDs/COX-2 inhibitors or calcium channel blockers, while subjects were taking neither NSAIDs/COX-2 inhibitors nor calcium channel blockers, and while subjects were not taking colchicine. In addition, adverse events while subjects were not taking colchicine for which subjects prematurely discontinued study drug were summarized. All adverse events that occurred in the groups described above

were summarized by MedDRA SOC, HLT, and preferred term. Fisher's exact test was used to perform pairwise comparisons between the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups for the groups with more than 5 subjects in each treatment group.

The numbers and percentages of subjects with potentially concerning laboratory values and elevated LFT values that occurred while subjects were not taking NSAIDs/COX-2 inhibitors were summarized. Fisher's exact test was used to perform pairwise comparisons between the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups. The numbers and percentages of subjects with elevated LFT values that occurred while subjects were not taking colchicine, while subjects were not taking NSAIDs/COX-2 inhibitors, and while subjects were taking neither NSAIDs/COX-2 inhibitors nor colchicine were summarized. Fisher's exact test was used to perform pairwise comparisons between the febuxostat 80 mg QD, febuxostat 120 mg QD, and allopurinol 300/100 mg QD treatment groups.

7.4.3 Causality Determination

The description of the adverse event included the date of onset, duration, severity, alternative etiology, the relationship of the event to the study drug as assessed by the investigator, any treatment required, and the outcome of the event. Categories associated with relationship to study drug (ie, definite, probable, possible, unlikely, and not related) are defined in **Table 61**.

Table 61 (Sponsor's Table 1.5b) Definitions for Investigator Assessment of Adverse Event Relationship to Study Drug

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

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Both doses proposed for marketing in this submission (80 mg and 120 mg) showed unacceptable safety profile, therefore the exploration of lower doses efficacy and safety would be recommended. Identification of the lowest effective dose would be desirable. However, since no strong dose-effect relationship was identified, establishing the safety of lower doses in long-term trials would be crucial.

8.2 Drug-Drug Interactions

Please, see ClinPharm review by Dennis Bashaw, Pharm.D.

8.3 Special Populations

Please, see ClinPharm review by Lei Zhang, Ph.D.

Subgroup analyses were performed for the demographic subgroups of age, gender, race, and BMI. In addition, analyses were performed for comorbidities which were either expected to have a higher prevalence in this population (renal insufficiency, cardiovascular disease, hypertension, congestive heart failure, diabetes, and hyperlipidemia) or which were selected because of safety-

related findings in the preclinical or clinical program (renal calculi, thyroid disease, and peripheral neuropathy).
No subject in the Phase 3 controlled studies had hepatic insufficiency, therefore the analysis is limited to a drug-disease interaction study in subjects with mild to moderate hepatic impairment.

Age

Phase 1 Study TMX-01-016

Study TMX-01-016 was a Phase 1, parallel-group, open-label, multiple-dose study in healthy subjects between the ages of 18 and 40, inclusive, and 65 years of age and older to evaluate the effect of gender and age on the safety, PD and PK of febuxostat when administered for 7 consecutive days. Forty-eight subjects were categorized based on age and gender and were randomized to receive febuxostat 80 mg QD for 7 consecutive days.
The PK and PD of febuxostat were not substantially affected by age (see Pharmacokinetic review).

The overall incidence of adverse events during dosing was higher for older subjects compared to younger subjects (58% and 29%, respectively). Similarly, the overall incidence of study drug-related adverse events was higher in older subjects compared to younger subjects (42% and 25%, respectively). Subjects ≥65 years of age had higher incidences of constipation and traumatic injury (29% and 8%, respectively) compared to subjects 18 to 40 years of age (13% and 0%, respectively). Conversely, subjects 18 to 40 years of age had a higher incidence of headache (8%) compared to subjects ≥65 years of age (4%). All reports of constipation were considered to be possibly related to study drug with alternate etiologies of changes in diet or food intolerance. All reports of headache were considered possibly related with an alternative etiology of tension headache. The majority of adverse events were mild in severity and considered to be possibly related to study drug. There were no deaths, serious adverse events, or premature discontinuations due to adverse events.

Phase 3 Controlled Studies

In the Phase 3 controlled studies, treatment-emergent adverse events were summarized by age (<45 years of age, 45-65 years of age, or >65 years of age). Within the febuxostat 80 mg QD treatment group, 71% of subjects <45 years of age, 76% of subjects 45-65 years of age, and 71% of subjects >65 years of age experienced at least 1 adverse event. In the febuxostat 120 mg QD group, 65% of subjects <45 years of age, 73% of those 45-65 years of age, and 78% of those >65 years of age experienced at least 1 adverse event. Seventy-eight percent (78%) of allopurinol 300/100 mg QD subjects <45 years of age, 78% of allopurinol 300/100 mg QD subjects 45-65 years of age, and 90% of allopurinol 300/100 mg QD subjects >65 years of age experienced at least 1 adverse event.
A summary of statistically significant differences in the most frequent (≥5% in any treatment group overall) treatment-emergent adverse events in the Phase 3 controlled studies is presented by age in **Table 62.**

No evidence of age-related increases in the most frequent adverse events was observed.

Table 62(Sponsor's Table 6.1a)
Statistically Significant Differences in Most Frequent Adverse Events by Age (Phase 3 Controlled Studies)

	Placebo			Febuxostat									Allopurinol		
		(N=134)		80 mg (N=523)			120 mg (N=520)			240 mg (N=134)			300/100 mg (N=521)		
MedDRA	<45	45-65	>65	<45	45-65	>65	<45	45-65	>65	<45	45-65	>65	<45	45-65	>65
High Level Term	(N=36)	(N=82)	(N=16)	(N=157)	(N=297)	(N=69)	(N=150)	(N=303)	(N=67)	(N=33)	(N=77)	(N=24)	(N=166)	(N=282)	(N=73)
Total Subjects with at Least 1 Adverse Event[a,b,m]	26 (72%)	58 (71%)	13 (81%)	112 (71%)	225 (76%)	49 (71%)	98 (65%)	222 (73%)	52 (78%)	20 (61%)	60 (78%)	18 (75%)	130 (78%)	219 (78%)	66 (90%)
Diarrhoea (Excl Infective)[d]	2 (6%)	7 (9%)	2 (13%)	16 (10%)	22 (7%)	5 (7%)	10 (7%)	28 (9%)	6 (9%)	3 (9%)	10 (13%)	5 (21%)	6 (4%)	17 (6%)	10 (14%)
Non-Site Specific Injuries NEC[f]	1 (3%)	1 (1%)	1 (6%)	2 (1%)	16 (5%)	5 (7%)	8 (5%)	9 (3%)	2 (3%)	0	7 (9%)	2 (8%)	5 (3%)	10 (4%)	5 (7%)
Nausea & Vomiting Symptoms[c,j]	0	5 (6%)	0	15 (10%)	11 (4%)	5 (7%)	8 (5%)	8 (3%)	7 (10%)	1 (3%)	7 (9%)	0	7 (4%)	4 (1%)	3 (4%)
Muscle Related Signs & Symptoms NEC[e]	1 (3%)	5 (6%)	1 (6%)	1 (<1%)	3 (1%)	2 (3%)	2 (1%)	1 (<1%)	1 (1%)	0	2 (3%)	0	2 (1%)	0	2 (3%)
Total Subjects with at Least 1 Treatment-related Adverse Event[a]	5 (14%)	22 (27%)	4 (25%)	36 (23%)	64 (22%)	19 (28%)	28 (19%)	67 (22%)	14 (21%)	7 (21%)	26 (34%)	6 (25%)	27 (16%)	52 (18%)	22 (30%)

Phase 3 studies included: C02-099 and C02-010 combined data.
NEC = not elsewhere classified
Note: Table displays incidence of most frequent (in ≥5% of subjects in any treatment group) treatment-emergent adverse events.
* Statistically significant difference among age groups in febuxostat 80 mg QD group ($p \leq 0.05$) using Fisher's exact test.
‡ Statistically significant difference among age groups in febuxostat 120 mg QD group ($p \leq 0.05$) using Fisher's exact test.
# Statistically significant difference among age groups in allopurinol 300/100 mg QD group ($p \leq 0.05$) using Fisher's exact test.
l Statistically significant difference between febuxostat 80 mg QD and allopurinol 300/100 mg QD ($p \leq 0.05$) using Cochran-Mantel-Haenszel test.
m Statistically significant difference between febuxostat 120 mg QD and allopurinol 300/100 mg QD ($p \leq 0.05$) using Cochran-Mantel-Haenszel test.
Cross-reference: Statistical Tables 6.1.1 and 6.2.1

After adjusting for age, statistically significant differences in the percent of subjects reporting **any adverse event** were found between the allopurinol 300/100 mg QD group and each of the febuxostat 80 mg QD and febuxostat 120 mg QD treatment groups.

Reviewer's comment:

- *Overall, the incidence of adverse reactions increases with age*

After adjusting for age, statistically significant differences were observed between the febuxostat 80 mg QD and allopurinol 300/100 mg QD treatment groups for the proportion of subjects with potentially concerning **high WBC and alkaline phosphatase** values. Additionally, statistically significant differences were observed between the febuxostat 120 mg QD and allopurinol 300/100 mg QD treatment groups for the proportion of subjects with potentially concerning **high PTT and glucose** values and between the febuxostat 80 mg QD and febuxostat 120 mg QD treatment groups for the proportion of subjects with potentially concerning **high urine glucose** values (**Table 63**). When there was no adjustment for age, the only laboratory tests for which there were statistically significant treatment group differences were for high **WBC, high PTT, and high urine glucose**.
The proportion of subjects with potentially concerning **high BUN** values was greatest among subjects >65 years of age; however, this pattern was consistent across all treatment groups.

Table 63 (Sponsor's Table 6.1b)
Statistically Significant Differences in Proportions of Subjects with Potentially Concerning Laboratory Values by Age (Phase 3 Controlled Studies)

	Placebo (N=134)			Febuxostat 80 mg (N=523)			Febuxostat 120 mg (N=520)			Febuxostat 240 mg (N=134)			Allopurinol 300/100 mg (N=521)		
Parameter - Criteria	<45	45-65	>65	<45	45-65	>65	<45	45-65	>65	<45	45-65	>65	<45	45-65	>65
Hematology	(N=32)	(N=76)	(N=14)	(N=142)	(N=283)	(N=66)	(N=141)	(N=283)	(N=67)	(N=30)	(N=70)	(N=21)	(N=158)	(N=266)	(N=69)
Hemoglobin - Low[‡,¶]	1 (3%)	2 (3%)	1 (7%)	5 (4%)	17 (6%)	9 (14%)	5 (4%)	12 (4%)	1 (1%)	1 (3%)	2 (3%)	0	3 (2%)	18 (7%)	7 (10%)
	N=32	N=76	N=14	N=142	N=283	N=66	N=140	N=283	N=67	N=30	N=70	N=21	N=158	N=265	N=69
Platelet Count - Low[¶]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2 (3%)
WBC Count - High[‡]	0	5 (7%)	0	6 (4%)	11 (4%)	0	2 (1%)	6 (2%)	4 (6%)	1 (3%)	0	1 (5%)	2 (1%)	5 (1%)	2 (3%)
Eosinophil Count - High[‡,¶]	1 (3%)	3 (4%)	0	6 (4%)	12 (4%)	8 (12%)	3 (6%)	11 (4%)	1 (1%)	1 (3%)	5 (7%)	0	6 (4%)	9 (3%)	9 (13%)
	N=29	N=74	N=13	N=130	N=252	N=59	N=125	N=256	N=66	N=28	N=59	N=19	N=147	N=252	N=62
PT - High[‡,¶]	1 (3%)	1 (1%)	1 (8%)	0	6 (2%)	4 (7%)	1 (<1%)	3 (1%)	6 (9%)	0	1 (2%)	0	0	3 (1%)	2 (3%)
	N=29	N=74	N=13	N=130	N=252	N=58	N=125	N=256	N=66	N=28	N=58	N=19	N=147	N=252	N=62
PTT - High[¶]	1 (3%)	0	1 (8%)	1 (<1%)	3 (1%)	1 (2%)	4 (3%)	3 (1%)	3 (5%)	0	0	1 (5%)	0	1 (<1%)	1 (2%)
Chemistry	(N=34)	(N=80)	(N=15)	(N=148)	(N=291)	(N=69)	(N=146)	(N=293)	(N=67)	(N=31)	(N=74)	(N=22)	(N=159)	(N=274)	(N=73)
Potassium - High[¶]	1 (3%)	1 (1%)	2 (13%)	0	3 (1%)	1 (1%)	0	2 (<1%)	2 (3%)	0	1 (1%)	2 (9%)	0	0	2 (3%)
Glucose - High[¶]	1 (3%)	2 (3%)	0	1 (<1%)	3 (1%)	2 (3%)	2 (1%)	4 (1%)	1 (1%)	0	1 (1%)	0	0	0	1 (1%)
BUN - High[‡,¶]	1 (3%)	3 (4%)	4 (27%)	1 (<1%)	22 (8%)	15 (22%)	4 (3%)	28 (10%)	12 (18%)	2 (6%)	11 (15%)	7 (32%)	1 (<1%)	17 (6%)	15 (23%)
Creatinine - High[‡,¶]	1 (3%)	6 (8%)	1 (7%)	1 (<1%)	12 (4%)	10 (14%)	3 (2%)	13 (4%)	9 (13%)	2 (6%)	4 (5%)	6 (27%)	4 (3%)	16 (6%)	9 (12%)
Alkaline Phosphatase - High[‡]	0	0	0	0	2 (<1%)	2 (3%)	0	0	1 (1%)	0	0	0	0	0	0
AST - High[‡]	2 (6%)	3 (4%)	1 (7%)	13 (9%)	23 (8%)	1 (1%)	18 (12%)	19 (6%)	1 (1%)	6 (19%)	4 (5%)	1 (5%)	13 (8%)	18 (7%)	3 (4%)
ALT - High[‡,¶]	3 (9%)	4 (5%)	1 (7%)	30 (20%)	29 (10%)	6 (9%)	32 (22%)	28 (10%)	5 (7%)	7 (23%)	3 (4%)	0	24 (15%)	22 (8%)	3 (4%)
Triglyceride - High[‡]	5 (15%)	10 (13%)	2 (13%)	23 (16%)	46 (16%)	4 (6%)	38 (26%)	39 (13%)	5 (7%)	8 (26%)	7 (9%)	2 (9%)	35 (22%)	42 (15%)	8 (11%)

Phase 3 studies included: CO2-009 and CO2-010 combined data.
† Statistically significant difference among age groups in febuxostat 80 mg QD group ($p \leq 0.05$) using Fisher's exact test.
‡ Statistically significant difference among age groups in febuxostat 120 mg QD group ($p \leq 0.05$) using Fisher's exact test.
§ Statistically significant difference among age groups in allopurinol 300/100 mg QD group ($p \leq 0.05$) using Fisher's exact test.
¶ Statistically significant difference between febuxostat 80 mg QD and allopurinol 300/100 mg QD ($p \geq 0.05$) using Cochran-Mantel-Haenszel test.
m Statistically significant difference between febuxostat 120 mg QD and allopurinol 300/100 mg QD ($p \geq 0.05$) using Cochran-Mantel-Haenszel test.
‡ Statistically significant difference between febuxostat 80 mg QD and febuxostat 120 mg QD ($p \geq 0.05$) using Cochran-Mantel-Haenszel test.
Cross-reference, Statistical Tables 6.4.1.1 and 6.4.2.1

	Placebo (N=134)			Febuxostat 80 mg (N=523)			Febuxostat 120 mg (N=520)			Febuxostat 240 mg (N=134)			Allopurinol 300/100 mg (N=521)		
Parameter - Criteria	<45	45-65	>65	<45	45-65	>65	<45	45-65	>65	<45	45-65	>65	<45	45-65	>65
Urinalysis	(N=32)	(N=76)	(N=14)	(N=142)	(N=282)	(N=66)	(N=140)	(N=282)	(N=67)	(N=30)	(N=70)	(N=21)	(N=158)	(N=266)	(N=69)
Glucose - High[‡]	1 (3%)	3 (4%)	0	1 (<1%)	4 (1%)	1 (2%)	5 (4%)	10 (4%)	1 (1%)	0	1 (1%)	0	3 (2%)	5 (2%)	4 (6%)
RBC - High[¶]	2 (6%)	1 (1%)	0	7 (5%)	14 (5%)	3 (5%)	6 (4%)	8 (3%)	5 (7%)	1 (3%)	3 (4%)	1 (5%)	3 (2%)	12 (5%)	8 (12%)

For the analyses of change from baseline in clinical laboratory values at Weeks 28 and 52, statistically significant treatment-by-age interactions were observed for **MCHC at Week 52 and for T_4 at Week 28**. The mean changes were small.

Reviewer's comments:

- *After age adjustment, additional statistically significant treatment differences were observed in the percent of subjects with potentially concerning high alkaline phosphatase and blood glucose values that were not observed in the analysis without adjusting for age, but due to the small sample size no definite conclusions can be made*
- *No dose adjustment of febuxostat is required based on age however, due to a high incidence of AEs in older population closer monitoring is always recommended*

Gender

Phase 1 Study TMX-01-016

The PK and PD of febuxostat were not substantially affected by gender in Study TMX-01-016.

The overall incidence of adverse events during dosing was higher in females than males (63% and 25%, respectively). Similarly, the overall incidence of study drug-related adverse events was higher in females than males (54% and 13%, respectively). Female subjects had higher incidences of constipation and headache (38% and 13%, respectively) compared to male subjects (4% and 0%, respectively). The majority of adverse events were mild in severity and considered to be possibly related to study drug. There were no deaths, serious adverse events, or premature discontinuations due to adverse events.

Phase 3 Controlled Studies

In the Phase 3 controlled studies, treatment-emergent adverse events were summarized by gender (male or female). Consistent with gout epidemiology, few female subjects were enrolled in the Phase 3 controlled studies. Ninety-three percent (93%) of female febuxostat 80 mg QD subjects and 73% of male febuxostat 80 mg QD subjects experienced at least 1 adverse event. Seventy-six percent (76%) of female febuxostat 120 mg QD subjects and 71% of male febuxostat 120 mg QD subjects experienced at least 1 adverse event. Ninety percent (90%) of female allopurinol 300/100 mg QD subjects and 79% of male allopurinol 300/100 mg QD subjects experienced at least 1 adverse event.

A summary of statistically significant differences in the most frequent (≥5% in any treatment group overall) treatment-emergent adverse events in the Phase 3 controlled studies is presented by gender in **Table 64.**

Table 64 (Sponsor's Table 6.1c) Statistically Significant Differences in Most Frequent Adverse Events by Gender (Phase 3 Controlled Studies)

	Placebo		Febuxostat						Allopurinol	
	(N=134)		80 mg (N=523)		120 mg (N=520)		240 mg (N=134)		300/100 mg (N=521)	
	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
MedDRA High Level Term	(N=11)	(N=123)	(N=29)	(N=494)	(N=21)	(N=499)	(N=8)	(N=126)	(N=29)	(N=492)
Total Subjects with at Least 1 Adverse Event[l,m]	8 (73%)	89 (72%)	27 (93%)	359 (73%)	16 (76%)	356 (71%)	7 (88%)	93 (74%)	26 (90%)	389 (79%)
Neurological Signs & Symptoms NEC*	1 (9%)	1 (<1%)	2 (7%)	20 (4%)	2 (10%)	12 (2%)	1 (13%)	8 (6%)	3 (10%)	10 (2%)
Gastrointestinal & Abdominal Pains (Excl Oral & Throat)†	0	3 (2%)	5 (17%)	10 (2%)	1 (5%)	13 (3%)	0	8 (6%)	0	12 (2%)
Nausea & Vomiting Symptoms†,‡	1 (9%)	4 (3%)	5 (17%)	26 (5%)	1 (5%)	22 (4%)	1 (13%)	7 (6%)	2 (7%)	12 (2%)
Vascular Hypertensive Disorders NEC†	2 (18%)	6 (5%)	4 (14%)	16 (3%)	0	16 (3%)	0	6 (5%)	0	17 (3%)
Total Subjects with at Least 1 Treatment-related Adverse Event	2 (18%)	29 (24%)	9 (31%)	110 (22%)	6 (29%)	103 (21%)	3 (38%)	36 (29%)	8 (28%)	93 (19%)

Phase 3 studies included: C02-009 and C02-010 combined data.
NEC = not elsewhere classified
Note: Table displays incidence of most frequent (in ≥5% of subjects in any treatment group) treatment-emergent adverse events.
? Statistically significant difference between genders in febuxostat 80 mg QD group ($p \leq 0.05$) using Fisher's exact test.
Statistically significant difference between genders in allopurinol 300/100 mg QD group ($p \leq 0.05$) using Fisher's exact test.
l Statistically significant difference between febuxostat 80 mg QD and allopurinol 300/100 mg QD ($p \leq 0.05$) using Cochran-Mantel-Haenszel test.
m Statistically significant difference between febuxostat 120 mg QD and allopurinol 300/100 mg QD ($p \leq 0.05$) using Cochran-Mantel-Haenszel test.
Cross-reference: Statistical Tables 6.1.2 and 6.2.2

After adjusting for gender, statistically significant differences were observed between each of the febuxostat 80 mg QD and 120 mg QD treatment groups and the allopurinol 300/100 mg QD treatment for the incidence of at least 1 **treatment-emergent** adverse event. After adjusting for gender, no statistically significant treatment differences were observed for the incidence of at least 1 **treatment-related** adverse event. These results are consistent with the comparisons between the treatment groups without adjusting for gender.

After adjusting for gender, statistically significant differences were observed between the febuxostat 80 mg QD and allopurinol 300/100 mg QD treatment groups for the proportion of subjects with potentially concerning high WBC or alkaline phosphatase values. Additionally, statistically significant differences were observed between the febuxostat 120 mg QD and allopurinol 300/100 mg QD treatment groups for the proportion of subjects with potentially concerning high PTT, or glucose values.

Statistically significant differences were also observed between the febuxostat 80 mg QD and 120 mg QD treatment groups for the proportion of subjects with potentially concerning low hemoglobin values and potentially concerning high urine glucose values **(Table 65)**. The statistically significant differences for WBC, PTT, and urine glucose are consistent with the analysis without adjusting for gender. For alkaline phosphatase, glucose, and hemoglobin values, no statistically significant treatment differences were observed in the analysis without adjusting for gender.

It appears that the small sample sizes for female subjects relative to male subjects and low frequencies contributed to the differences in the statistical significance **(Table 65)**.

Table 65 (Sponsor's Table 6.1d) Statistically Significant Differences in Proportions of Subjects with Potentially Concerning Laboratory Values by Gender (Phase 3 Controlled Studies)

	Placebo		Febuxostat						Allopurinol	
	(N=134)		80 mg (N=523)		120 mg (N=520)		240 mg (N=134)		300/100 mg (N=521)	
Parameter - Criteria	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Hematology	(N=9)	(N=113)	(N=28)	(N=463)	(N=21)	(N=470)	(N=6)	(N=115)	(N=26)	(N=467)
Hemoglobin - Low[f]	2 (22%)	2 (2%)	0	31 (7%)	0	18 (4%)	0	3 (3%)	1 (4%)	27 (6%)
WBC - High[f]	1 (11%)	4 (4%)	3 (11%)	14 (3%)	0	12 (3%)	0	2 (2%)	0	7 (1%)
	(N=9)	(N=107)	(N=24)	(N=416)	(N=20)	(N=427)	(N=5)	(N=100)	(N=25)	(N=436)
PTT - High[f,m]	0	2 (2%)	0	5 (1%)	3 (15%)	7 (2%)	0	1 (1%)	0	2 (<1%)
Chemistry	(N=11)	(N=118)	(N=28)	(N=480)	(N=21)	(N=485)	(N=7)	(N=120)	(N=28)	(N=478)
Glucose - High[f,m]	0	3 (3%)	2 (7%)	4 (<1%)	0	7 (1%)	0	1 (<1%)	0	1 (<1%)
BUN - High[f,g]	1 (9%)	7 (6%)	7 (25%)	31 (6%)	4 (19%)	40 (8%)	4 (57%)	16 (13%)	8 (29%)	25 (5%)
Creatinine - High[f]	1 (9%)	7 (6%)	4 (14%)	19 (4%)	2 (10%)	25 (5%)	1 (14%)	11 (9%)	3 (11%)	26 (5%)
Alkaline Phosphatase - High[f]	0	0	1 (4%)	3 (<1%)	0	1 (<1%)	0	0	0	0
Endocrinology	(N=8)	(N=100)	(N=20)	(N=382)	(N=17)	(N=383)	(N=5)	(N=91)	(N=25)	(N=408)
TSH - High[g]	0	0	1 (5%)	7 (2%)	0	10 (3%)	0	1 (1%)	3 (12%)	9 (2%)
	(N=8)	(N=100)	(N=20)	(N=382)	(N=16)	(N=383)	(N=5)	(N=90)	(N=25)	(N=407)
T_4 - High[f,g]	0	0	1 (5%)	0	1 (6%)	0	0	0	0	0
Urinalysis	(N=9)	(N=113)	(N=28)	(N=462)	(N=21)	(N=468)	(N=6)	(N=115)	(N=26)	(N=467)
Protein - High[g]	2 (22%)	4 (4%)	3 (11%)	18 (4%)	1 (5%)	19 (4%)	0	7 (6%)	4 (15%)	22 (5%)
Glucose - High[f]	0	4 (4%)	1 (4%)	5 (1%)	0	16 (3%)	0	1 (<1%)	0	12 (3%)
RBC - High[f,g]	0	3 (3%)	4 (14%)	20 (4%)	3 (14%)	16 (3%)	1 (17%)	4 (3%)	5 (19%)	18 (4%)
WBC - High[f,g]	3 (33%)	2 (2%)	6 (21%)	9 (2%)	6 (29%)	12 (3%)	1 (17%)	5 (4%)	7 (27%)	15 (3%)

Phase 3 studies included: C02-009 and C02-010 combined data.
† Statistically significant difference between genders in febuxostat 80 mg QD group ($p \leq 0.05$) using Fisher's exact test.
‡ Statistically significant difference between genders in febuxostat 120 mg QD group ($p \leq 0.05$) using Fisher's exact test.
# Statistically significant difference between genders in allopurinol 300/100 mg QD group ($p \leq 0.05$) using Fisher's exact test.
f Statistically significant difference between febuxostat 80 mg QD and allopurinol 300/100 mg QD ($p \leq 0.05$) using Cochran-Mantel-Haenszel test.
m Statistically significant difference between febuxostat 120 mg QD and allopurinol 300/100 mg QD ($p \leq 0.05$) using Cochran-Mantel-Haenszel test.
g Statistically significant difference between febuxostat 80 mg QD and febuxostat 120 mg QD ($p \leq 0.05$) using Cochran-Mantel-Haenszel test.
Cross-reference: Statistical Tables 6.4.1.2 and 6.4.2.2

For the analysis of mean changes from baseline to the Week 28 and Week 52 Visits for clinical laboratory parameters, a statistically significant interaction between gender and treatment was observed for alkaline phosphatase and calcium at Week 28 and for LDH at Week 52. For

alkaline phosphatase, a mean decrease in the febuxostat 120 mg QD treatment and a mean increase in the allopurinol 300/100 mg QD treatment group at Week 28 were observed. For LDH, the small number of female subjects, as well as an imbalance in the numbers of female subjects across the treatment groups at Week 52 appears to contribute to the significance of interaction.

In summary, in the Phase 1 PK study, the PK and PD of febuxostat were not substantially affected by gender. The overall incidence of adverse events and study drug-related adverse events during dosing in the Phase 1 study was higher in females than males.

In the Phase 3 controlled studies, the overall incidences of **treatment-emergent** adverse events were higher for female subjects than for male subjects for each of the treatment groups. The statistically significant treatment differences for overall incidences of treatment-emergent adverse events after adjusting for gender are consistent with the comparisons between the treatment groups without adjusting for gender.
The overall incidences of **treatment-related adverse** events were higher for female subjects than for male subjects for each of the treatment groups, with the exception of the placebo group.
No dose adjustment of febuxostat is required based on gender.

Race

Phase 3 Controlled Studies

In the Phase 3 controlled studies, treatment-emergent adverse events were summarized by race. Due to the small number of subjects in each of non-Caucasian races, these subjects were combined and referred to as others in one of the statistical analyses. A second summarization was performed by the race subgroups of Asian, Black, Caucasian, Hispanic, and others. No statistical comparison was performed in this second analysis.

Seventy-six percent (76%) of Caucasian febuxostat 80 mg QD subjects and 68% of febuxostat 80 mg QD subjects of other races experienced at least 1 adverse event. Seventy-two percent (72%) of Caucasian febuxostat 120 mg QD subjects and 69% of febuxostat 120 mg QD subjects of other races experienced at least 1 adverse event. Eighty percent (80%) of Caucasian allopurinol 300/100 mg QD subjects and 78% of allopurinol 300/100 mg QD subjects of other races experienced at least 1 adverse event (**Table 66**).
After adjusting for race (Caucasian, others), statistically significant differences were observed between each of the febuxostat 80 mg QD and 120 mg QD treatment groups and the allopurinol 300/100 mg QD treatment group for the incidence of at least 1 **treatment-emergent** adverse event. These differences were also statistically significant without adjusting for race.

A summary of statistically significant differences in the most common (≥5% in any treatment group overall) treatment-emergent adverse events in the Phase 3 controlled studies is presented by race in **Table 66**.

Table 66 (Sponsor's Table 6.1e) Statistically Significant Differences in Most Frequent Adverse Events by Race (Phase 3 Controlled Studies)

	Placebo		Febuxostat						Allopurinol	
	(N=134)		80 mg (N=523)		120 mg (N=520)		240 mg (N=134)		300/100 mg (N=521)	
MedDRA High Level Term	Caucasian (N=108)	Others (N=26)	Caucasian (N=393)	Others (N=130)	Caucasian (N=413)	Others (N=107)	Caucasian (N=107)	Others (N=27)	Caucasian (N=401)	Others (N=120)
Total Subjects with at Least 1 Adverse Event[1a]	82 (76%)	15 (58%)	297 (76%)	89 (68%)	298 (72%)	74 (69%)	75 (70%)	23 (85%)	322 (80%)	93 (78%)
Diarrhoea (Excl Infective)[†]	11 (10%)	0	39 (10%)	4 (3%)	37 (9%)	7 (7%)	15 (14%)	3 (11%)	24 (6%)	9 (8%)
Nausea & Vomiting Symptoms[‡]	4 (4%)	1 (4%)	25 (6%)	6 (5%)	19 (5%)	4 (4%)	6 (6%)	2 (7%)	10 (2%)	4 (3%)
Total Subjects with at Least 1 Treatment-related Adverse Event	24 (22%)	7 (27%)	93 (24%)	26 (20%)	93 (23%)	16 (15%)	32 (30%)	7 (26%)	84 (21%)	17 (14%)

Phase 3 studies included: C02-009 and C02-010 combined data.
Note: Table displays incidence of most frequent (in ≥5% of subjects in any treatment group) treatment-emergent adverse events.
† Statistically significant difference between races in febuxostat 80 mg QD group ($p \leq 0.05$) using Fisher's exact test.
‡ Statistically significant difference between febuxostat 80 mg QD and allopurinol 300/100 mg QD ($p \leq 0.05$) using Cochran-Mantel-Haenszel test.
a Statistically significant difference between febuxostat 120 mg QD and allopurinol 300/100 mg QD ($p \leq 0.05$) using Cochran-Mantel-Haenszel test.
Cross-reference: Statistical Tables 6.1.3.1 and 6.2.3

After adjusting for race (Caucasian, others), no statistically significant differences were observed for the incidence of at least 1 **treatment-related** adverse event. This is similar to what was observed in the unadjusted analysis of treatment-related adverse events.
Too few subjects in each treatment group were Asian (n=1 to 18), Black (n=9 to 62), Hispanic (n=8 to 36), or of other races (n=4 to 21), to draw meaningful conclusions regarding the incidence of adverse events by these racial subgroups.

After adjusting for race (Caucasian, others), statistically significant differences were observed between the febuxostat 80 mg QD and allopurinol 300/100 mg QD treatment groups for the proportion of subjects with potentially concerning high WBC or alkaline phosphatase values. Additionally, statistically significant differences were observed between the febuxostat 120 mg QD and allopurinol 300/100 mg QD treatment groups for the proportion of subjects with potentially concerning high PTT or glucose values. A statistically significant difference was also observed between the febuxostat 80 mg QD and 120 mg QD treatment groups for the proportion of subjects with potentially concerning high urine glucose values (**Table 67**). When no adjustment was made for race (Caucasian, others), the only laboratory tests for which there were statistically significant treatment group differences in the percent of subjects with potentially concerning values were high WBC, high PTT, and high urine glucose.

Table 67 (Sponsor's Table 6.1f) Statistically Significant Differences in Proportions of Subjects with Potentially Concerning Laboratory Values by Race (Phase 3 Controlled Studies)

Parameter - Criteria	Placebo (N=134)		Febuxostat 80 mg (N=523)		Febuxostat 120 mg (N=520)		Febuxostat 240 mg (N=134)		Allopurinol 300/100 mg (N=521)	
	Caucasian	Others	Caucasian	Others	Caucasian	Others	Caucasian	Others	Caucasian	Others
Hematology	(N=98)	(N=24)	(N=371)	(N=120)	(N=391)	(N=100)	(N=96)	(N=25)	(N=383)	(N=110)
WBC - High[l]	3 (3%)	2 (8%)	11 (3%)	6 (5%)	8 (2%)	4 (4%)	2 (2%)	0	6 (2%)	1 (<1%)
Neutrophils - Low[‡]	0	0	5 (1%)	2 (2%)	1 (<1%)	5 (5%)	0	1 (4%)	4 (1%)	4 (4%)
	(N=94)	(N=22)	(N=340)	(N=100)	(N=358)	(N=89)	(N=82)	(N=23)	(N=363)	(N=98)
PTT - High[m]	1 (1%)	1 (5%)	4 (1%)	1 (1%)	6 (2%)	4 (4%)	1 (1%)	0	2 (<1%)	0
Chemistry	(N=104)	(N=25)	(N=382)	(N=126)	(N=405)	(N=101)	(N=102)	(N=25)	(N=392)	(N=114)
Glucose - High[m]	3 (3%)	0	3 (<1%)	3 (2%)	6 (1%)	1 (<1%)	0	1 (4%)	1 (<1%)	0
Creatinine - High[‡]	7 (7%)	1 (4%)	15 (4%)	8 (6%)	17 (4%)	10 (10%)	10 (10%)	2 (8%)	21 (5%)	8 (7%)
Alkaline Phosphatase - High[‡]	0	0	3 (<1%)	1 (<1%)	1 (<1%)	0	0	0	0	0
AST - High[ψ]	7 (7%)	0	25 (7%)	10 (8%)	31 (8%)	7 (7%)	10 (10%)	1 (4%)	21 (5%)	13 (11%)
Endocrinology	(N=89)	(N=19)	(N=312)	(N=90)	(N=318)	(N=81)	(N=76)	(N=19)	(N=345)	(N=88)
T_4 - Low[ψ]	0	0	1 (<1%)	1 (1%)	1 (<1%)	0	0	0	0	2 (2%)
Urinalysis	(N=98)	(N=24)	(N=370)	(N=120)	(N=389)	(N=100)	(N=96)	(N=25)	(N=383)	(N=110)
Glucose - High[†]	3 (3%)	1 (4%)	4 (1%)	2 (2%)	15 (4%)	1 (1%)	1 (1%)	0	10 (3%)	2 (2%)
WBC - High[§]	3 (3%)	2 (8%)	12 (3%)	3 (3%)	14 (4%)	4 (4%)	5 (5%)	1 (4%)	12 (3%)	10 (9%)

Phase 3 studies included: C02-009 and C02-010 combined data.
‡ Statistically significant difference between races in febuxostat 120 mg QD group ($p \leq 0.05$) using Fisher's exact test.
ψ Statistically significant difference between races in allopurinol 300/100 mg QD group ($p \leq 0.05$) using Fisher's exact test.
l Statistically significant difference between febuxostat 80 mg QD and allopurinol 300/100 mg QD ($p \leq 0.05$) using Cochran-Mantel-Haenszel test.
m Statistically significant difference between febuxostat 120 mg QD and allopurinol 300/100 mg QD ($p \leq 0.05$) using Cochran-Mantel-Haenszel test.
† Statistically significant difference between febuxostat 80 mg QD and febuxostat 120 mg QD ($p \leq 0.05$) using Cochran-Mantel-Haenszel test.
Cross-reference: Statistical Tables 6.4.1.3 and 6.4.2.3

For the analysis of changes from baseline to Week 28 and Week 52 Visits for clinical laboratory parameters, statistically significant interactions between race (Caucasian, others) and treatment were observed for sodium at Week 28, for eosinophils, TSH and glucose at Week 52, and for MCH at Weeks 28 and 52. The significant interaction for sodium appears to be due to a greater mean decrease in other races in the febuxostat 80 mg QD group compared to greater mean decreases in Caucasians in the allopurinol 300/100 mg QD group. The mean changes for these parameters were small and were not considered to be clinically meaningful.

In summary, a statistically significant treatment difference in the overall incidence of adverse events was observed between each of the febuxostat 80 mg QD and febuxostat 120 mg QD treatment groups and the allopurinol 300/100 mg QD treatment group after adjusting for race (Caucasian, others). No statistically significant difference was observed for the overall incidence of **treatment-related** adverse events between any treatment groups after adjusting for race. These results are consistent with the comparisons between the treatment groups without adjusting for race.

The Sponsor's Conclusion:
Although the majority of subjects were Caucasian, race did not appear to adversely affect the safety of febuxostat.

Baseline Body Mass Index

Phase 3 Controlled Studies

In the Phase 3 controlled studies, treatment-emergent adverse events were summarized by baseline BMI (18.5-<25 kg/m2, 25-<30 kg/m2, or ≥30 kg/m2). Eighty percent (80%) of febuxostat 80 mg QD subjects with a baseline BMI between 18.5-<25 kg/m2, 67% of febuxostat 80 mg QD subjects with a baseline BMI between 25-<30 kg/m2, and 77% of febuxostat 80 mg QD subjects with a baseline BMI ≥30 kg/m2 experienced at least

1 adverse event. Sixty-one percent (61%) of febuxostat 120 mg QD subjects with a baseline BMI between 18.5-<25 kg/m2, 73% of febuxostat 120 mg QD subjects with a baseline BMI between 25-<30 kg/m2, and 72% of febuxostat 120 mg QD subjects with a baseline BMI ≥30 kg/m2 experienced at least 1 adverse event. Eighty-two percent (82%) of allopurinol 300/100 mg QD subjects with a baseline BMI between 18.5-<25 kg/m2, 79% of allopurinol 300/100 mg QD subjects with a baseline BMI between 25-<30 kg/m2, and 80% of allopurinol 300/100 mg QD subjects with a baseline BMI ≥30 kg/m2 experienced at least 1 adverse event.

After adjusting for baseline BMI, statistically significant differences were observed between each of the febuxostat 80 mg QD and 120 mg QD treatment groups and the allopurinol 300/100 mg QD treatment group for the incidence of at least 1 treatment-emergent adverse event. These treatment differences were also observed when no adjustment for BMI was made.
A summary of statistically significant differences in the most common (≥5% in any treatment group overall) treatment-emergent adverse events in the Phase 3 controlled studies is presented by baseline BMI in **Table 68.**

Table 68 (Sponsor's Table 6.1g) Statistically Significant Differences in Most Frequent Adverse Events by Baseline Body Mass Index (Phase 3 Controlled Studies)

	Placebo (N=134)			Febuxostat 80 mg (N=523)			Febuxostat 120 mg (N=519)			Febuxostat 240 mg (N=134)			Allopurinol 300/100 mg (N=517)		
	BMI (kg/m²)			BMI (kg/m²)			BMI (kg/m²)			BMI (kg/m²)			BMI (kg/m²)		
MedDRA High Level Term	18.5-<25 (N=16)	25-<30 (N=48)	≥30 (N=70)	18.5-<25 (N=25)	25-<30 (N=160)	≥30 (N=338)	18.5-<25 (N=23)	25-<30 (N=168)	≥30 (N=328)	18.5-<25 (N=9)	25-<30 (N=42)	≥30 (N=83)	18.5-<25 (N=22)	25-<30 (N=180)	≥30 (N=315)
Total Subjects with at Least 1 Adverse Event[1a]	11 (69%)	32 (67%)	54 (77%)	20 (80%)	107 (67%)	259 (77%)	14 (61%)	122 (73%)	255 (78%)	7 (78%)	28 (67%)	63 (76%)	18 (82%)	142 (79%)	251 (80%)
Nausea & Vomiting Symptoms[1]	1 (6%)	0	4 (6%)	1 (4%)	9 (6%)	21 (6%)	2 (9%)	8 (5%)	15 (4%)	0	3 (7%)	5 (6%)	0	8 (4%)	6 (2%)
Total Subjects with at Least 1 Treatment-related Adverse Event	4 (25%)	14 (29%)	15 (21%)	6 (24%)	52 (32%)	81 (24%)	5 (22%)	34 (20%)	69 (21%)	2 (22%)	12 (29%)	24 (30%)	3 (14%)	42 (23%)	55 (17%)

Phase 3 studies included: CO2-009 and CO2-010 combined data.
Note: Five subjects (1 febuxostat 120 mg QD and 4 allopurinol 300/100 mg QD) did not have BMI data. Table displays incidence of most frequent (in ≥5% of subjects in any treatment group) treatment-emergent adverse events.
1 Statistically significant difference between febuxostat 80 mg QD and allopurinol 300/100 mg QD (p≥0.05) using Cochran-Mantel-Haenszel test.
1a Statistically significant difference between febuxostat 120 mg QD and allopurinol 300/100 mg QD (p≥0.05) using Cochran-Mantel-Haenszel test.
Cross-reference: Statistical Tables 6.1.4 and 6.2.4

No statistically significant differences were observed for the incidence of at least 1 **treatment-related** adverse event. This is consistent with the unadjusted evaluation of treatment-related adverse events.

After adjusting for baseline BMI, statistically significant differences were observed between the febuxostat 80 mg QD and allopurinol 300/100 mg QD treatment groups for the proportion of subjects with potentially concerning high WBC or alkaline phosphatase values. Additionally, statistically significant differences were observed between the febuxostat 120 mg QD and allopurinol 300/100 mg QD treatment groups for the proportion of subjects with potentially concerning high PTT or glucose values. A statistically significant difference was also observed between the febuxostat 80 mg QD and 120 mg QD treatment groups for the proportion of subjects with potentially concerning high urine glucose values (**Table 69).** For alkaline phosphatase and glucose, no statistically significant treatment differences were observed in the analysis without adjusting for BMI. It appears that the small sample size in the low BMI groups and low frequencies contributed to the differences in the statistical significance.

When analyzing changes from baseline in hematology, chemistry, endocrinology, or urinalysis parameters at Weeks 28 and 52, statistically significant treatment-by-BMI interactions were observed for reticulocytes, amylase and FT_4 at Week 28, and for hemoglobin, hematocrit, RBC, and total T_4 at Week 52. However, the changes observed in the treatment groups and BMI categories were small and not considered clinically meaningful.

Table 69 (Sponsor's Table 6.1h) Statistically Significant Differences in Proportions of Subjects with Potentially Concerning Laboratory Values by Baseline Body Mass Index (Phase 3 Controlled Studies)

	Placebo			Febuxostat									Allopurinol		
	(N=134)			80 mg (N=523)			120 mg (N=519)			240 mg (N=134)			300/100 mg (N=517)		
	BMI (kg/m²)			BMI (kg/m²)			BMI (kg/m²)			BMI (kg/m²)			BMI (kg/m²)		
Parameter - Criteria	18.5-<25	25-<30	≥30	18.5-<25	25-<30	≥30	18.5-<25	25-<30	≥30	18.5-<25	25-<30	≥30	18.5-<25	25-<30	≥30
Hematology	(N=16)	(N=42)	(N=64)	(N=24)	(N=148)	(N=319)	(N=23)	(N=158)	(N=310)	(N=8)	(N=37)	(N=76)	(N=21)	(N=167)	(N=301)
WBC - High[1]	1 (6%) (N=16)	0 (N=40)	4 (6%) (N=60)	2 (8%) (N=22)	5 (3%) (N=137)	10 (3%) (N=282)	1 (4%) (N=20)	2 (1%) (N=142)	9 (3%) (N=285)	1 (13%) (N=8)	1 (3%) (N=32)	0 (N=66)	0 (N=19)	2 (1%) (N=156)	5 (2%) (N=283)
PT - High[3]	0 (N=16)	1 (3%) (N=40)	2 (3%) (N=60)	0 (N=22)	2 (1%) (N=137)	8 (3%) (N=281)	1 (5%) (N=20)	3 (2%) (N=142)	6 (2%) (N=285)	0 (N=8)	1 (3%) (N=31)	0 (N=66)	0 (N=19)	4 (3%) (N=156)	0 (N=283)
PTT - High[3]	0	0	2 (3%)	0	3 (2%)	2 (<1%)	1 (5%)	3 (2%)	6 (2%)	1 (13%)	0	0	0	2 (1%)	0
Chemistry	(N=16)	(N=46)	(N=67)	(N=25)	(N=156)	(N=327)	(N=23)	(N=165)	(N=320)	(N=8)	(N=39)	(N=80)	(N=22)	(N=175)	(N=305)
Sodium - High[1]	0	0	1 (1%)	3 (12%)	0	2 (<1%)	1 (4%)	1 (<1%)	1 (<1%)	0	0	0	0	2 (1%)	1 (<1%)
Potassium - High[1]	1 (6%)	3 (7%)	0	2 (8%)	1 (<1%)	1 (<1%)	1 (4%)	2 (1%)	1 (<1%)	2 (25%)	1 (3%)	0	0	2 (1%)	0
Glucose - High[2]	0	0	3 (4%)	0	2 (1%)	4 (1%)	0	2 (1%)	5 (2%)	0	0	1 (1%)	0	0	1 (<1%)
Creatinine - High[1]	1 (6%)	3 (7%)	4 (6%)	1 (4%)	5 (3%)	19 (6%)	3 (13%)	15 (8%)	11 (3%)	0	4 (10%)	8 (10%)	3 (14%)	10 (6%)	16 (5%)
Total Bilirubin - High[3]	0	0	1 (1%)	1 (4%)	2 (1%)	1 (<1%)	0	3 (2%)	7 (2%)	0	1 (3%)	3 (4%)	2 (9%)	3 (2%)	0
Alkaline Phosphatase - High[1,3]	0	0	0	0	1 (<1%)	3 (<1%)	1 (4%)	0	0	0	0	0	0	0	0
AST - High[3]	1 (6%)	4 (9%)	2 (3%)	4 (16%)	13 (8%)	18 (6%)	1 (4%)	8 (5%)	28 (9%)	1 (13%)	4 (10%)	6 (8%)	4 (18%)	14 (8%)	14 (5%)
Urinalysis	(N=16)	(N=42)	(N=64)	(N=24)	(N=148)	(N=318)	(N=23)	(N=159)	(N=308)	(N=8)	(N=37)	(N=76)	(N=21)	(N=167)	(N=301)
Glucose - High[1]	0	1 (2%)	3 (5%)	0	3 (2%)	5 (<1%)	0	6 (4%)	10 (3%)	0	1 (3%)	0	0	4 (2%)	8 (3%)

Phase 3 studies included: C02-009 and C02-011 combined data.
Note: Five subjects (1 febuxostat 120 mg QD and 4 allopurinol 300/100 mg QD) did not have BMI data.
† Statistically significant difference among body mass index groups in febuxostat 80 mg QD group ($p \leq 0.05$) using Fisher's exact test.
‡ Statistically significant difference among body mass index groups in febuxostat 120 mg QD group ($p \leq 0.05$) using Fisher's exact test.
* Statistically significant difference among body mass index groups in allopurinol 300/100 mg QD group ($p \leq 0.05$) using Fisher's exact test.
1 Statistically significant difference between febuxostat 80 mg QD and allopurinol 300/100 mg QD ($p \geq 0.05$) using Cochran-Mantel-Haenszel test.
2 Statistically significant difference between febuxostat 120 mg QD and allopurinol 300/100 mg QD ($p \leq 0.05$) using Cochran-Mantel-Haenszel test.
3 Statistically significant difference between febuxostat 80 mg QD and febuxostat 120 mg QD ($p \leq 0.05$) using Cochran-Mantel-Haenszel test.
Cross-reference: Statistical Tables 6.4.1.4 and 6.4.2.4

In summary, there was no specific trend in the overall incidences of adverse events in relation to baseline BMI across the treatment groups. Adjustment for BMI did not affect the statistically significant differences between the allopurinol 300/100 mg QD, febuxostat 80 mg QD, and febuxostat 120 mg QD treatment groups in the overall incidences of **treatment-emergent and treatment-related** adverse events.

The Sponsor's Conclusion:
Body mass index of subjects did not adversely affect the safety of febuxostat.

Renal Insufficiency

Phase 1 Study TMX-01-008

Study TMX-01-008 was a Phase 1, parallel-group, open-label, multiple-dose study to evaluate the safety, PK and PD profile of febuxostat after 7 consecutive days of 80 mg QD dosing in subjects with varying degrees of renal impairment (mild, moderate, or severe) and subjects with normal renal function. Male and female subjects between 30 and 70 years of age, inclusive, were categorized by their renal function status, which was based on the measured Cl_{cr} on Day -1

(Cockcroft-Gault method). Gender and age balancing among renal function groups was attempted.
Although there were changes in the PK of febuxostat, the percent decrease in serum urate appeared to be similar regardless of renal function.

Thirty-two subjects received febuxostat 80 mg QD for 7 consecutive days. The overall incidence of adverse events was 55%, 50%, 57%, and 88% in the normal, mild, moderate, and severe renal impairment groups, respectively. The most common adverse events were ecchymosis, headache, vasodilatation (flushing, feeling of warmth), diarrhea, back pain, and injection site hemorrhage. All adverse events were either mild or moderate in severity. The incidence of **treatment-related** adverse events was 36%, 17%, 43%, and 25% in the normal, mild, moderate, and severe renal impairment groups, respectively.

Phase 3 Controlled Studies

In the Phase 3 controlled studies, **treatment-emergent** adverse events were summarized by history of renal insufficiency using both serum creatinine value (>1.5 mg/dL) (yes or no) and calculated Cl_{cr} (<80 mL/minute) (yes or no).

In the Phase 3 controlled studies, febuxostat dosing was not adjusted based upon renal function. In contrast, the allopurinol dose (100 mg QD or 300 mg QD) was determined based upon serum creatinine levels in Study C02-009.

Based on Serum Creatinine

In the Phase 3 controlled studies, 47 subjects (3 placebo, 11 febuxostat 80 mg QD, 15 febuxostat 120 mg QD, 7 febuxostat 240 mg QD, and 11 allopurinol 300/100 mg QD) had renal insufficiency, defined as a baseline serum creatinine value >1.5 mg/dL. Due to the small sample sizes, results should be interpreted with caution.

Seventy-four percent of febuxostat 80 mg QD subjects without renal insufficiency and 82% of febuxostat 80 mg QD subjects with renal insufficiency experienced at least 1 adverse event. Seventy-two percent of febuxostat 120 mg QD subjects without renal insufficiency and 53% of febuxostat 120 mg QD subjects with renal insufficiency experienced at least 1 adverse event. Eighty percent (80%) of allopurinol 300/100 mg QD subjects without renal insufficiency and 82% of allopurinol 300/100 mg QD subjects with renal insufficiency experienced at least 1 adverse event.
A summary of statistically significant differences in the most common (≥5% in any treatment group overall) treatment-emergent adverse events in the Phase 3 controlled studies is presented by renal insufficiency status in **Table 70**.

Table 70 (Sponsor's Table 6.1i) Statistically Significant Differences in Most Frequent Adverse Events by History of Renal Insufficiency Based on Serum Creatinine >1.5 mg/dL (Phase 3 Controlled Studies)

	Placebo		Febuxostat						Allopurinol	
	(N=134)		80 mg (N=523)		120 mg (N=520)		240 mg (N=134)		300/100 mg (N=521)	
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
MedDRA High Level Term	(N=131)	(N=3)	(N=512)	(N=11)	(N=505)	(N=15)	(N=127)	(N=7)	(N=510)	(N=11)
Total Subjects with at Least 1 Adverse Event[1,m]	94 (72%)	3 (100%)	377 (74%)	9 (82%)	364 (72%)	8 (53%)	93 (73%)	5 (71%)	406 (80%)	9 (82%)
Upper Respiratory Tract Infections[‡]	21 (16%)	0	112 (22%)	4 (36%)	105 (21%)	0	25 (20%)	2 (29%)	121 (24%)	3 (27%)
Nausea & Vomiting Symptoms[1]	5 (4%)	0	29 (6%)	2 (18%)	23 (5%)	0	8 (6%)	0	13 (3%)	1 (9%)
Total Subjects with at Least 1 Treatment-related Adverse Event	31 (24%)	0	114 (22%)	5 (45%)	105 (21%)	4 (27%)	37 (29%)	2 (29%)	100 (20%)	1 (9%)

Phase 3 studies included: C02-009 and C02-010 combined data.
Note: Table displays incidence of most frequent (in ≥5% of subjects in any treatment group) treatment-emergent adverse events.
‡ Statistically significant difference among renal history groups in febuxostat 120 mg QD group ($p \leq 0.05$) using Fisher's exact test.
1 Statistically significant difference between febuxostat 80 mg QD and allopurinol 300/100 mg QD ($p \leq 0.05$) using Cochran-Mantel-Haenszel test.
m Statistically significant difference between febuxostat 120 mg QD and allopurinol 300/100 mg QD ($p \leq 0.05$) using Cochran-Mantel-Haenszel test.
Cross-reference: Statistical Tables 6.5.1.1 and 6.6.1.1

After adjusting for renal insufficiency status based on serum creatinine, statistically significant differences were observed between each of the febuxostat 80 mg QD and 120 mg QD treatment groups and the allopurinol 300/100 mg QD treatment group for the incidence of at least 1 treatment-emergent adverse event. After adjusting for renal insufficiency status based on serum creatinine, no statistically significant treatment differences were observed for the incidence of at least 1 treatment-related adverse event. These results are consistent with the comparisons between the treatment groups without adjusting for renal insufficiency status based on serum creatinine.

For subjects identified as having renal insufficiency status based on serum creatinine, a statistically significant difference was observed between the febuxostat 120 mg QD and allopurinol 300/100 mg QD treatment groups for the proportion of subjects with potentially concerning urine protein values.
This is different from the analyses for the whole population where no statistically significant treatment differences were observed for potentially concerning urine protein values. It appears that the small sample sizes and low frequencies contributed to the difference in the statistical significance.

For subjects with renal insufficiency, statistically significant treatment differences in mean changes from baseline to Week 28 were observed for hematocrit, glucose, AST, ALT, and urine pH. The small number of subjects with renal insufficiency as measured by serum creatinine in the mean change analyses prevents any clinically meaningful interpretation.

Based on Calculated Creatinine Clearance

In the Phase 3 controlled studies, 643 subjects (45 placebo, 183 febuxostat 80 mg QD, 184 febuxostat 120 mg QD, 51 febuxostat 240 mg QD, and 180 allopurinol 300/100 mg QD) had renal insufficiency, defined as a calculated Cl_{cr} <80 mL/minute.

Seventy-two percent of febuxostat 80 mg QD subjects without renal insufficiency and 77% of febuxostat 80 mg QD subjects with renal insufficiency experienced at least 1 adverse event. Seventy-two percent of febuxostat 120 mg QD subjects without renal insufficiency and 71% of febuxostat 120 mg QD subjects with renal insufficiency experienced at least 1 adverse event. Seventy-nine percent of allopurinol 300/100 mg QD subjects without renal insufficiency

and 80% of allopurinol 300/100 mg QD subjects with renal insufficiency experienced at least 1 adverse event.

After adjusting for renal insufficiency status based on calculated Cl_{cr}, statistically significant differences were observed between each of the febuxostat 80 mg QD and 120 mg QD treatment groups and the allopurinol 300/100 mg QD treatment group for the incidence of at least 1 treatment-emergent adverse event. Furthermore, after adjusting for renal insufficiency status based on calculated Cl_{cr}, a statistically significant difference was observed between the febuxostat 80 mg QD and allopurinol 300/100 mg QD treatment groups for the incidence of **nausea and vomiting symptoms**. These results are consistent with the treatment comparisons when no adjustment was made for renal insufficiency based on calculated Cl_{cr}. A summary of statistically significant differences in the most common (≥5% in any treatment group overall) treatment-emergent adverse events in the Phase 3 controlled studies is presented by renal insufficiency status in **Table 71**.

Table 71 (Sponsor's Table 6.1j)
Statistically Significant Differences in Most Frequent Adverse Events by History of Renal Insufficiency Based on Calculated Creatinine Clearance <80 mL/minute (Phase 3 Controlled Studies)

	Placebo (N=134)		Febuxostat 80 mg (N=523)		Febuxostat 120 mg (N=519)		Febuxostat 240 mg (N=134)		Allopurinol 300/100 mg (N=517)	
MedDRA High Level Term	No (N=89)	Yes (N=45)	No (N=340)	Yes (N=183)	No (N=335)	Yes (N=184)	No (N=83)	Yes (N=51)	No (N=337)	Yes (N=180)
Total Subjects with at Least 1 Adverse Event[1m]	62 (70%)	35 (78%)	245 (72%)	141 (77%)	240 (72%)	131 (71%)	56 (67%)	42 (82%)	267 (79%)	144 (80%)
Joint Related Signs & Symptoms[‡]	3 (3%)	4 (9%)	26 (8%)	30 (16%)	33 (10%)	22 (12%)	3 (4%)	4 (8%)	37 (11%)	20 (11%)
Nausea & Vomiting Symptoms[‡#]	3 (3%)	2 (4%)	18 (5%)	13 (7%)	10 (3%)	13 (7%)	3 (4%)	5 (10%)	8 (2%)	6 (3%)
Headaches NEC[‡,*]	6 (7%)	1 (2%)	26 (8%)	11 (6%)	29 (9%)	7 (4%)	8 (10%)	4 (8%)	34 (10%)	7 (4%)
Total Subjects with at Least 1 Treatment-related Adverse Event[1]	24 (27%)	7 (16%)	67 (20%)	52 (28%)	67 (20%)	41 (22%)	23 (28%)	16 (31%)	61 (18%)	39 (22%)

Phase 3 studies included: C02-009 and C02-010 combined data.
Note: Table displays incidence of most frequent (in ≥5% of subjects in any treatment group) treatment-emergent adverse events.
‡ Statistically significant difference among renal history groups in febuxostat 80 mg QD group ($p \leq 0.05$) using Fisher's exact test.
‡ Statistically significant difference among renal history groups in febuxostat 120 mg QD group ($p \leq 0.05$) using Fisher's exact test.
# Statistically significant difference among renal history groups in allopurinol 300/100 mg QD group ($p \leq 0.05$) using Fisher's exact test.
1 Statistically significant difference between febuxostat 80 mg QD and allopurinol 300/100 mg QD ($p \leq 0.05$) using Cochran-Mantel-Haenszel test.
m Statistically significant difference between febuxostat 120 mg QD and allopurinol 300/100 mg QD ($p \leq 0.05$) using Cochran-Mantel-Haenszel test.
Cross-reference: Statistical Tables 6.5.1.2 and 6.6.1.2

For treatment-related adverse events, after adjusting for renal insufficiency status based on calculated Cl_{cr}, no statistically significant differences were observed between treatment groups for the incidence of at least 1 treatment-related adverse event (**Table 71**). These results are consistent with the treatment comparisons when no adjustment was made for renal insufficiency based on calculated Cl_{cr}.

Although there were changes in the PK of febuxostat, the percent decrease in serum urate appeared to be similar regardless of renal function.
In the Phase 3 controlled studies, the number of subjects with a history of renal insufficiency as measured by serum creatinine was too small to produce statistically meaningful comparisons

between the treatment groups for adverse events, mean change from baseline, and potentially concerning values for clinical laboratory parameters.

For mild renal insufficiency as measured by calculated Cl_{cr}, the overall incidences of treatment-emergent adverse events were similar for subjects with and without renal insufficiency within each of the treatment groups. The statistically significant treatment differences for overall incidences of treatment-emergent adverse events after adjusting for renal insufficiency status are consistent with the comparisons between the treatment groups without adjusting for renal insufficiency status.

The Sponsor's Conclusion:
Based on the results of a PK/PD study, no dose adjustment of febuxostat is required in subjects with impaired renal function.

A history of renal insufficiency as measured by calculated Cl_{cr} did not adversely affect the safety of febuxostat.

Hepatic Insufficiency

Febuxostat is extensively metabolized by conjugation via the UDP-GT enzyme system and oxidation via the cytochrome P450 (CYP) system. The oxidation of the isobutyl side chain leads to the formation of 4 pharmacologically active hydroxy metabolites, 3 of which are measurable in plasma of subjects receiving single or multiple oral doses of febuxostat. In vitro studies with human liver microsomes showed that those oxidative metabolites were formed by CYP1A1, CYP1A2, CYP2C8 or CYP2C9 and febuxostat glucuronide (major metabolite) was formed by UDP-GT 1A2, 1A8, and 1A9.

Phase 1 Study TMX-01-012

Study TMX-01-012 was a Phase 1, parallel-group, open-label, multiple-dose study to compare the safety, PK, and PD profile of febuxostat in subjects with hepatic impairment to subjects with normal hepatic function. Subjects with hepatic impairment were entered into the study at a rate similar to the enrollment rate of subjects with normal hepatic function. Twenty-eight male and female subjects (non-pregnant, non-lactating) between 30 and 70 years of age, inclusive, were placed into study groups based on the Child-Pugh Classification of their hepatic function: normal, mildly impaired, or moderately impaired.

An attempt was made to enroll subjects in the normal hepatic function group who matched subjects in each of the impaired hepatic function groups with respect to gender, weight (± 10 kg) and age (± 4 years). Each subject received febuxostat 80 mg QD for 7 consecutive days.

The PK and PD of febuxostat were not substantially affected by mild or moderate hepatic impairment in Study TMX-01-012. The incidence of adverse events was higher in the mild and moderate hepatic impairment groups (63% and 75%, respectively) compared to the normal hepatic function group (25%). No single adverse event was reported in more than 1 subject in the

normal hepatic function group. The number of adverse events occurring in more than 1 subject was greatest in the body as a whole system for subjects with mild hepatic impairment (abdominal pain [25%] and headache [25%]). The number of adverse events occurring in more than 1 subject in the moderate hepatic impairment group was greatest in the digestive (diarrhea [25%]) and urogenital systems (urinary frequency [25%]). Headache only occurred in subjects with mild impairment (25%), as well as those with normal hepatic function (8%) and nausea, dizziness and pharyngitis only occurred in subjects with either mild or moderate impairment (13% each), but in no subjects with normal hepatic function. All adverse events in any hepatic function group were mild in severity and most were considered possibly, probably, or definitely related to study drug. There were no deaths, serious adverse events, or premature terminations as the result of an adverse event.

Phase 3 Controlled Studies

In the Phase 3 controlled studies, subjects with active liver disease or hepatic dysfunction defined as ALT and AST >1.5 x ULN were excluded from participation in the studies.
No subject had a medical history of hepatic insufficiency in the Phase 3 controlled studies.

In summary, results from the Phase 1 PK study indicated that mild or moderate hepatic impairment did not significantly impair the PK and PD of febuxostat therefore no dose adjustment of febuxostat is required in subjects with mild or moderate hepatic impairment. No data are available for subjects with severe hepatic impairment. However, caution should be exercised in subjects with severe hepatic impairment.

No subject had a medical history of hepatic insufficiency in the Phase 3 controlled studies.

Renal Calculi

The majority of subjects in each treatment group did not have a history of renal calculi (**Table 72**). Of note, renal calculi was an exclusion criterion in Study C02-009.
The overall incidence of treatment-emergent adverse events ranged from 33-81% across treatment groups for subjects with a history of renal calculi and from 72-80% across treatment groups for subjects without a history of renal calculi (**Table 72**).
A summary of statistically significant differences in the most frequent (≥5% in any treatment group overall) treatment-emergent adverse events in the Phase 3 controlled studies is presented by history of renal calculi in **Table 72**.

Table 72 (Sponsor's Table 6.1l)
Statistically Significant Differences in Most Frequent Adverse Events by History of Renal Calculi
(Phase 3 Controlled Studies)

	Placebo		Febuxostat						Allopurinol	
	(N=134)		80 mg (N=523)		120 mg (N=520)		240 mg (N=134)		300/100 mg (N=521)	
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
MedDRA High Level Term	(N=131)	(N=3)	(N=497)	(N=26)	(N=494)	(N=26)	(N=131)	(N=3)	(N=494)	(N=27)
Total Subjects with at Least 1 Adverse Event[‡#]	96 (73%)	1 (33%)	365 (73%)	21 (81%)	355 (72%)	17 (65%)	96 (73%)	2 (67%)	396 (80%)	19 (70%)
Musculoskeletal & Connective Tissue Signs & Symptoms[¶]	13 (10%)	0	55 (11%)	3 (12%)	59 (12%)	3 (12%)	14 (11%)	0	56 (11%)	9 (33%)
Nausea & Vomiting Symptoms[¶]	5 (4%)	0	30 (6%)	1 (4%)	18 (4%)	5 (19%)	9 (6%)	0	14 (3%)	0
Total Subjects with at Least 1 Treatment-related Adverse Event	30 (23%)	1 (33%)	112 (23%)	7 (27%)	104 (21%)	5 (19%)	37 (28%)	2 (67%)	96 (19%)	5 (19%)

Phase 3 studies included: CO2-089 and CO2-010 combined data

Note: Table displays incidence of most frequent (in ≥5% of subjects in any treatment group) treatment-emergent adverse events that had a statistically significant treatment-by-subgroup interaction.

‡ Statistically significant difference between renal calculi history groups in febuxostat 120 mg QD group ($p \leq 0.05$) using Fisher's exact test.

Statistically significant difference between renal calculi history groups in allopurinol 300/100 mg QD group ($p \leq 0.05$) using Fisher's exact test.

¶ Statistically significant difference between febuxostat 80 mg QD and allopurinol 300/100 mg QD ($p \leq 0.05$) using Cochran-Mantel-Haenszel test.

m Statistically significant difference between febuxostat 120 mg QD and allopurinol 300/100 mg QD ($p \leq 0.05$) using Cochran-Mantel-Haenszel test.

Cross-reference: Statistical Tables 6.5.3 and 6.6.3

A statistically significant difference in the overall incidence of treatment-emergent adverse events was observed between each of the febuxostat 80 mg QD and febuxostat 120 mg QD treatment groups and the allopurinol 300/100 mg QD treatment group after adjusting for history of renal calculi (**Table 72**). No statistically significant treatment differences were observed for the overall incidence of treatment-related adverse events (Table 68). These results are consistent with the comparisons between the treatment groups without adjusting for history of renal calculi.

For subjects with a history of renal calculi, no statistically significant differences were observed between the treatment groups for potentially concerning laboratory parameters.
For the mean changes from baseline to Week 28 and Week 52 Visits for clinical laboratory parameters, the sample size for subjects with history of renal calculi was too small to perform a meaningful analysis.

The Sponsor's Conclusion:
A history of renal calculi did not appear to adversely affect the safety of febuxostat; however, the small number of subjects with a history of renal calculi precludes meaningful conclusions.

Atherosclerotic Disease

The majority of subjects in each treatment group did not have a history of atherosclerotic disease (**Table 73**).
In each treatment group, the overall incidence of treatment-emergent adverse events ranged from 71-86% for subjects with a history of atherosclerotic disease and from 69-80% for subjects without a history of atherosclerotic disease (**Table 73**).

A summary of statistically significant differences in the most common (≥5% in any treatment group overall) treatment-emergent adverse events in the Phase 3 controlled studies is presented by history of atherosclerotic disease in **Table 73**.

Table 73 (Sponsor's Table 6.1n) Statistically Significant Differences in Most Frequent Adverse Events by History of Atherosclerotic Disease (Phase 3 Controlled Studies)

	Placebo		Febuxostat						Allopurinol	
	(N=134)		80 mg (N=523)		120 mg (N=520)		240 mg (N=134)		300/100 mg (N=521)	
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
MedDRA High Level Term	(N=116)	(N=18)	(N=462)	(N=61)	(N=455)	(N=65)	(N=110)	(N=24)	(N=471)	(N=50)
Total Subjects with at Least 1 Adverse Event[‡,#,ł,ת]	83 (72%)	14 (78%)	340 (74%)	46 (75%)	316 (69%)	56 (86%)	81 (74%)	17 (71%)	377 (80%)	38 (76%)
Diarrhoea (Excl Infective)[ł]	10 (9%)	1 (6%)	35 (8%)	8 (13%)	33 (7%)	11 (17%)	15 (14%)	3 (13%)	29 (6%)	4 (8%)
Headaches NEC[#]	7 (6%)	0	33 (7%)	4 (7%)	34 (7%)	3 (5%)	12 (11%)	0	41 (9%)	0
Gastrointestinal & Abdominal Pains (Excl Oral & Throat)[#]	3 (3%)	0	13 (3%)	2 (3%)	10 (2%)	4 (6%)	7 (6%)	1 (4%)	8 (2%)	4 (8%)
Nausea & Vomiting Symptoms[ł]	4 (3%)	1 (6%)	25 (5%)	6 (10%)	20 (4%)	3 (5%)	7 (6%)	1 (4%)	13 (3%)	1 (2%)
Total Subjects with at Least 1 Treatment-related Adverse Event	28 (24%)	3 (17%)	100 (22%)	19 (31%)	98 (22%)	11 (17%)	34 (31%)	5 (21%)	92 (20%)	9 (18%)

Phase 3 studies included: C02-009 and C02-010 combined data

Note: Table displays incidence of most frequent (in ≥5% of subjects in any treatment group) treatment-emergent adverse events that had a statistically significant treatment-by-subgroup interaction.

‡ Statistically significant difference between atherosclerotic disease history groups in febuxostat 120 mg QD group ($p \leq 0.05$) using Fisher's exact test.

Statistically significant difference between atherosclerotic disease history groups in allopurinol 300/100 mg QD group ($p \leq 0.05$) using Fisher's exact test.

ł Statistically significant difference between febuxostat 80 mg QD and allopurinol 300/100 mg QD ($p \leq 0.05$) using Cochran-Mantel-Haenszel test.

ת Statistically significant difference between febuxostat 120 mg QD and allopurinol 300/100 mg QD ($p \leq 0.05$) using Cochran-Mantel-Haenszel test.

Cross-reference: Statistical Tables 6.3.5 and 6.6.5

A statistically significant difference in the overall incidence of treatment-emergent adverse events was observed between each of the febuxostat 80 mg QD and febuxostat 120 mg QD treatment groups and the allopurinol 300/100 mg QD treatment group after adjusting for history of atherosclerotic disease (**Table 73**).

No statistically significant treatment differences were observed for the overall incidence of treatment-related adverse events after adjusting for history of atherosclerotic disease (**Table 73**). These results are consistent with the comparisons between the treatment groups without adjusting for history of atherosclerotic disease.

No statistically significant differences were observed between the treatment groups for potentially concerning laboratory parameters among subjects with a history of atherosclerotic disease.

For the mean change from baseline analyses for subjects with atherosclerotic disease, statistically significant differences in mean change from baseline to Week 28 and/or Week 52 were observed between the febuxostat 80 mg QD and allopurinol 300/100 mg treatment groups for MCH, platelet count, basophils, measured Cl_{cr}, and inorganic phosphorus. Statistically significant differences were observed between the febuxostat 120 mg QD and allopurinol 300/100 mg QD treatment groups for platelet count, neutrophils, basophils, measured Cl_{cr}, total cholesterol, and total T_3. Additionally, a statistically significant difference was observed between the febuxostat 80 mg QD and febuxostat 120 mg QD treatment groups for WBC, neutrophils, and total T_3. However, these mean changes were small and not considered to be clinically meaningful.

The Sponsor's conclusion: A history of atherosclerotic disease did not appear to adversely affect the safety of febuxostat.

Reviewer's comments:

- *Despite the Sponsor's conclusion that the history of atherosclerotic disease did not adversely affect the safety of febuxostat, this reviewer disagree with its conclusion on the following grounds:*
- *It appears that there is some difference in the incidence of overall adverse events between the subgroups with and without a history of CV disease.*
- *Furthermore, the table # 73 included data from phase 3 trials only, and omitted data from phase two trials.*
- *Analysis was done for the most frequent AEs only (>5%); those events do not include cardio-vascular AEs since the incidence of CV events in the current dataset is about 2 %*
- *Since the history of CV disease poses a higher risk of subsequent CV events, therefore this would be a high risk populaiton for CV events in general. The Sponsor did not address whether or not the history of cardio-vascular disease adversely affects the cardio-vascular safety of febuxostat which is a major concern of this review. Therefore the Sponsor's conclusion is misleading.*

Hypertension

In each treatment group, the overall incidence of treatment-emergent adverse events in subjects with a history of hypertension was similar to that in subjects without a history of hypertension (**Table 74**).

A summary of statistically significant differences in the most common (≥5% in any treatment group overall) treatment-emergent adverse events in the Phase 3 controlled studies is presented by history of hypertension in **Table 74.**

Table 74 (Sponsor's Table 6.1o)
Statistically Significant Differences in Most Frequent Adverse Events by History of Hypertension
(Phase 3 Controlled Studies)

	Placebo		Febuxostat						Allopurinol	
	(N=134)		80 mg (N=523)		120 mg (N=520)		240 mg (N=134)		300/100 mg (N=521)	
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
MedDRA High Level Term	(N=73)	(N=61)	(N=293)	(N=230)	(N=283)	(N=237)	(N=64)	(N=70)	(N=286)	(N=235)
Total Subjects with at Least 1 Adverse Event[1,n]	51 (70%)	46 (75%)	213 (73%)	173 (75%)	202 (71%)	170 (72%)	43 (67%)	55 (79%)	225 (79%)	190 (81%)
Joint Related Signs & Symptoms[‡]	5 (7%)	2 (3%)	30 (10%)	26 (11%)	22 (8%)	33 (14%)	0	7 (10%)	29 (10%)	28 (12%)
Nausea & Vomiting Symptoms[†]	3 (4%)	2 (3%)	15 (5%)	16 (7%)	9 (3%)	14 (6%)	3 (5%)	5 (7%)	11 (4%)	3 (1%)
Vascular Hypertensive Disorders NEC[*]	4 (5%)	4 (7)	6 (2%)	14 (6%)	6 (2%)	10 (4%)	2 (3%)	4 (6%)	9 (3%)	8 (3%)
Total Subjects with at Least 1 Treatment-related Adverse Event	19 (26%)	12 (20%)	64 (22%)	55 (24%)	57 (20%)	52 (22%)	17 (27%)	22 (31%)	51 (18%)	50 (21%)

Phase 3 studies included: C02-009 and C02-010 combined data
Note: Table displays incidence of most frequent (in ≥5% of subjects in any treatment group) treatment-emergent adverse events that had a statistically significant treatment-by-subgroup interaction.
* Statistically significant difference between hypertension history groups in febuxostat 80 mg QD group ($p \leq 0.05$) using Fisher's exact test.
‡ Statistically significant difference between hypertension history groups in febuxostat 120 mg QD group ($p \leq 0.05$) using Fisher's exact test.
† Statistically significant difference between febuxostat 80 mg QD and allopurinol 300/100 mg QD ($p \leq 0.05$) using Cochran-Mantel-Haenszel test.
n Statistically significant difference between febuxostat 120 mg QD and allopurinol 300/100 mg QD ($p \leq 0.05$) using Cochran-Mantel-Haenszel test.
Cross-reference: Statistical Tables 6.5.6 and 6.6.6

A statistically significant difference in the overall incidence of treatment-emergent adverse events was observed between each of the febuxostat 80 mg QD and febuxostat 120 mg QD treatment groups and the allopurinol 300/100 mg QD treatment group after adjusting for history of hypertension **(Table 74).** No statistically significant treatment differences were observed for the overall incidence of treatment-related adverse events after adjusting for history of hypertension (**Table 74**). These results are consistent with the comparisons between the treatment groups without adjusting for history of hypertension.

For subjects with a history of hypertension, statistically significant differences were observed between the febuxostat 120 mg QD and allopurinol 300/100 mg QD treatment groups for the proportion of subjects with potentially concerning PTT (high) values, and between the febuxostat 80 mg QD and febuxostat 120 mg QD treatment groups for the proportion of subjects with potentially concerning hemoglobin and total bilirubin values.

The statistically significant difference for PTT is consistent with the analysis for the whole population, while no statistically significant treatment difference was observed in the analysis of total bilirubin for the whole population . For subjects with a history of hypertension, a higher proportion of subjects with potentially concerning total bilirubin values was observed in the febuxostat 120 mg QD treatment group compared to the febuxostat 80 mg QD treatment group.

For the mean change from baseline analyses for subjects with a history of hypertension, statistically significant differences in mean change from baseline to Week 28 and/or Week 52 were observed between the febuxostat 80 mg QD and allopurinol 300/100 mg treatment groups for RBC, MCV, MCH, platelet count, neutrophils, alkaline phosphatase, AST, ALT, and total cholesterol. Statistically significant differences were observed between the febuxostat 120 mg QD and allopurinol 300/100 mg QD treatment groups for MCV, MCH, platelet count, total bilirubin, alkaline phosphatase, ALT, total cholesterol, and total T_4. Additionally, a statistically significant difference was observed between the febuxostat 80 mg QD and febuxostat 120 mg QD treatment groups for alkaline phosphatase and urine specific gravity. However, these mean changes were small and not considered to be clinically meaningful.

The Sponsor's Conclusion: A history of hypertension did not adversely affect the safety of febuxostat.

Congestive Heart Failure

In the Phase 3 controlled studies, few subjects had a history of congestive heart failure: 11 febuxostat 80 mg QD, 10 febuxostat 120 mg QD, 8 allopurinol 300/100 mg QD, 6 febuxostat 240 mg QD, and 5 placebo.

In each treatment group, the overall incidence of treatment-emergent adverse events ranged from 50-100% for subjects with a history of congestive heart failure and from 71-79% for subjects without a history of congestive heart failure (**Table 75**).

A summary of statistically significant differences in the most common (≥5% in any treatment group overall) treatment-emergent adverse events in the Phase 3 controlled studies is presented by history of congestive heart failure in **Table 75**.

Table 75 (Sponsor's Table 6.1p) Statistically Significant Differences in Most Frequent Adverse Events by History of Congestive Heart Failure (Phase 3 Controlled Studies)

	Placebo (N=134)		Febuxostat 80 mg (N=523)		Febuxostat 120 mg (N=520)		Febuxostat 240 mg (N=134)		Allopurinol 300/100 mg (N=521)	
MedDRA High Level Term	No (N=129)	Yes (N=5)	No (N=512)	Yes (N=11)	No (N=510)	Yes (N=10)	No (N=128)	Yes (N=6)	No (N=513)	Yes (N=8)
Total Subjects with at Least 1 Adverse Event[1m]	94 (73%)	3 (60%)	377 (74%)	9 (82%)	364 (71%)	8 (80%)	95 (74%)	3 (50%)	407 (79%)	8 (100%)
Nausea & Vomiting Symptoms[1]	5 (4%)	0	31 (6%)	0	23 (5%)	0	8 (6%)	0	13 (3%)	1 (13%)
Total Subjects with at Least 1 Treatment-related Adverse Event	31 (24%)	0	117 (23%)	2 (18%)	107 (21%)	2 (20%)	37 (29%)	2 (33%)	98 (19%)	3 (38%)

Phase 3 studies included: C02-009 and C02-010 combined data

Note: Table displays incidence of most frequent (in ≥5% of subjects in any treatment group) treatment-emergent adverse events that had a statistically significant treatment-by-subgroup interaction.

1 Statistically significant difference between febuxostat 80 mg QD and allopurinol 300/100 mg QD ($p \leq 0.05$) using Cochran-Mantel-Haenszel test.

m Statistically significant difference between febuxostat 120 mg QD and allopurinol 300/100 mg QD ($p \leq 0.05$) using Cochran-Mantel-Haenszel test.

Cross-reference: Statistical Tables 6.5.7 and 6.6.7

Statistically significant differences in the overall incidence of treatment-emergent adverse events were observed between each of the febuxostat 80 mg QD and febuxostat 120 mg QD treatment groups and the allopurinol 300/100 mg QD treatment group after adjusting for history of congestive heart failure (**Table 75**). No statistically significant treatment differences were observed for the overall incidence of treatment-related adverse events (**Table 75**). These results are consistent with the comparisons between the treatment groups without adjusting for history of congestive heart failure.

No statistically significant differences were observed between the treatment groups for potentially concerning laboratory parameters among subjects with a history of congestive heart failure.

The sample size for subjects with congestive heart failure was too small to perform a meaningful analysis of the mean change from baseline for the laboratory parameters.

The Sponsor's Conclusion:
A history of congestive heart failure did not adversely affect the safety of febuxostat; however, the small number of subjects with a history of congestive heart failure precludes meaningful conclusions.

8.4 Pediatrics

Not applicable

8.5 Advisory Committee Meeting

None

8.6 Literature Review

None

8.7 Postmarketing Risk Management Plan

Will not be discussed at this time

8.8 Other Relevant Materials

None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Tatiana Oussova
9/22/2005 10:30:24 AM
MEDICAL OFFICER

Joel Schiffenbauer
9/23/2005 10:16:24 AM
MEDICAL OFFICER
see MO/TL review for my recommendations

9/12/05

Efficacy

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-856
Submission Code	N-000
Letter Date	12/14/2004
Stamp Date	12/15/2004
PDUFA Goal Date	10/15/2005
Reviewer Name	Joel Schiffenbauer
Review Completion Date	9/07/05
Established Name	Febuxostat
(Proposed) Trade Name	Uloric
Therapeutic Class	Xanthine oxidase inhibitor
Applicant	TAP Pharmaceuticals
Priority Designation	S
Formulation	Oral
Dosing Regimen	80 or 120 mg daily
Indication	Hyperuricemia associated with gout
Intended Population	Adults

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1. Executive Summary

This Executive Summary will serve as a review of the entire NDA. The remainder of this review presents the evidentiary basis for efficacy (by Dr. Joel Schiffenbauer). For a discussion of safety issues, the reader is referred to the separate safety review by Dr. Tatiana Oussova.

1.1Recommendation on Regulatory Action

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

The sponsor should be requested to provide additional efficacy and safety data preferably from an additional trial or trials as follows: the sponsor should address the issue of cardiovascular safety; it is likely that a large outcome study will be required. The sponsor should be requested to provide additional efficacy data based on the previously defined primary outcome, for the 40 and 240 mg doses (the 40 mg dose for efficacy with possibly greater safety, and the 240 mg dose for greater efficacy including clinically important outcomes such as number of gouty flares). As part of the clinical efficacy data, clinical outcome such as gouty attacks and tophi size should be evaluated for all doses (including the 40 mg dose). Additional information on subjects with renal insufficiency should also be provided with these studies.

Therefore, based on the above assessments, the risk/benefit analysis is not favorable for this drug at this time. However, it is recommended that an approvable action be taken based on the demonstrated efficacy and because of the need for additional safety information.

1.2Recommendation on Postmarketing Actions

See 1.2.2 "Required phase 4 commitments" section.

1.2.1Risk Management Activity

This drug is not recommended for approval at this time. Therefore no postmarketing risk management activities are recommended at this time.

1.2.2Required Phase 4 Commitments

b(4)

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

. A long term clinical study should also be performed to identify whether the number of gout flares is reduced. There are no commitments related to PREA that need to be addressed for the indication that was sought in this NDA. Drug interaction studies with warfarin, theophylline and azathioprine should also be undertaken. Additional studies in individuals with renal impairment should also be performed.

1.2.3Other Phase 4 Requests

There are no additional phase 4 requests at this time.

1.3Summary of Clinical Findings

1.3.1Brief Overview of Clinical Program

Febuxostat (Uloric) is an oral anti-hyperuricemic drug to be used in patients for the management of hyperuricemia associated with gout. The clinical development program for febuxostat in the United States was comprised of 24 PK Phase 1 studies, 2 Phase 2 studies, and 3 Phase 3 studies (2 pivotal studies for efficacy).Two of these studies (1 Phase 2 and 1 Phase 3) are extension studies and are currently ongoing. In addition, the licensing partner for TAP, Teijin, conducted a clinical development program consisting of 15 clinical trials in Japan in a different patient population with doses lower than those developed in the United States (up to 40 mg in Japan).

There was 1 supportive phase II dose ranging study, and 2 pivotal phase III efficacy trials submitted in this NDA which serve as the primary basis for determining the efficacy of the drug. The phase II study was a 28 day study that examined the effects of 40, 80 and 120 mg febuxostat on serum uric acid levels using 2 different methods of determining uric acid levels. The first of the 2 phase III studies was a 6 month placebo and active comparator (allopurinol) controlled trial consisting of 1072 subjects, and utilized 80, 120 and 240 mg doses of febuxostat. The second phase III study was a one year active comparator controlled trial consisting of 760 subjects and studied 80 and 120 mg doses of febuxostat compared to allopurinol.

In the United States clinical program, a total of 2518 subjects received at least 1 dose of febuxostat. Nine hundred ninety-four subjects were exposed to any dose of febuxostat for ≥6 months and 433 were exposed for 12 months. As for the febuxostat 80 mg QD dose, 1629 subjects were exposed to at least 1 dose and 530 and 230 subjects were exposed for ≥6 and ≥12 months, respectively. As for the febuxostat 120 mg QD dose, 1012 subjects received at least 1 dose and 396 and 153 were exposed for 6 and 12 months, respectively. The extent of exposure in

the febuxostat clinical development program is considered sufficient to assess both the short- and long-term safety of febuxostat and these numbers exceed the number of subjects exposed in clinical studies recommended by ICH guidelines.

There was no postmarketing data used in the evaluation of this product.

1.3.2Efficacy

There were 2 pivotal efficacy trials including a 6 month active and placebo controlled trial and a one year active control only trial. The primary endpoint of both trials was the number of subjects with uric acid level less than 6 mg/dL for the last 3 visits. The 6 mg/dL level was chosen based on data (from the literature) supporting this level as the limit of solubility of uric acid, and the correlation of reduction of the number of gouty attacks and tophi size with reduction of serum urate levels below this level. Reduction below this level therefore allows for uric acid to be released from body stores, resulting in a net excretion of excess uric acid. The sponsor discussed this endpoint with the Division, and it was further discussed and accepted as an endpoint at an Arthritis Advisory Meeting in June 2004. This endpoint utilizing the last 3 visits was chosen (rather than, for instance, the number of subjects with uric acid less than 6 at the last visit only) in order to ensure that subjects not only had a uric acid less than 6, but that it was sustained. Sustained uric acid levels of less than 6 mg/dL are felt to be the sine qua non for adequate treatment of hyperuricemia associated with gout.

An alternative endpoint such as number of gouty attacks could have been chosen as the primary endpoint. This was not used because the literature and practice strongly support the approach to treatment of hyperuricemia associated with gout that was chosen here. However, the sponsor did provide additional data to examine the incidence of gouty attacks and tophi size and number, in both trials.

The duration of the pivotal trials (6 months and one year) was such as to provide robust evidence of both efficacy and safety. The sponsor also provided data (albeit somewhat limited) for the 240 mg dose for both efficacy and safety, even though the 240 mg is not proposed as a labeled dose. However, data for the 40 mg dose is limited to only the results of a single phase II one month trial. The population studied appears to represent the majority of patients likely to take febuxostat, with the exception that data in a renally impaired population is limited. However, although the sponsor did perform a specific study in renally impaired individuals this was a short PK/PD study and does not provide robust data for the long term safety of this drug in this population.

Based on the primary outcome, febuxostat was demonstrated to be efficacious (see Table 2 in the integrated summary of efficacy-this review). Furthermore, multiple secondary analyses support the efficacy of the drug (see Table 3 and subsequent tables; also see tables in the 10. Appendices for each study, 009 and 010). For example an additional analysis examining the number of subjects with uric acid less than 6 for every visit after the first 4 weeks also supported efficacy of

the drug. This is an even higher bar than the primary endpoint, as these individuals had uric acid levels consistently less than 6 mg/dL. Although these trials were not designed to address this issue, there were fewer gouty attacks over the course of the trials. However, for the 6 month trial that utilized a placebo arm, there was no statistical difference between the drug and placebo. Therefore, although the number of attacks was similar between febuxostat and allopurinol in the second phase III trial (a one year, non-inferiority trial with no placebo comparator), a conclusion that febuxostat reduces the number of clinical attacks of gout cannot be reached. It is likely that trials of longer duration are needed to definitively address this question. Consideration should be given to asking the sponsor to obtain this data in the postmarketing period if the drug is approved.

Both of the pivotal efficacy studies included allopurinol as the comparator and in both instances febuxostat was demonstrated to be significantly more efficacious. An analysis of allopurinol tablets collected from the sponsor, demonstrated that the allopurinol met specifications and was therefore acceptable as the comparator.

Febuxostat, if approved, would be the second xanthine oxidase inhibitor (after allopurinol) to be used for the chronic treatment of hyperuricemia.

1.3.3 Safety

There are however, a number of safety concerns with the use of febuxostat raised by the data presented in this NDA (phase II and III studies). These concerns will be summarized here. For a more complete discussion of safety related issues, the reader is referred to Dr. T. Oussova's safety review.

First, across the entire NDA data base there were eight deaths (please see Table of deaths in Dr. Oussova's review; also sponsor's Table 3.3a in the safety update report[SUR]). All occurred in the febuxostat treatment arm. There were no deaths in the allopurinol comparator arm. There were 2 MIs and 2 cases of respiratory failure with febuxostat. There were also 2 cases of retroperitoneal hemorrhage, both in the febuxostat treatment group (in addition to these 2 deaths due to retroperitoneal hemorrhage there was one SAE, and one increased INR reported as an SAE with febuxostat and none with allopurinol).

Second, across the entire NDA data base there were more cardiovascular thromboembolic events in the febuxostat treatment group compared to either placebo or allopurinol (please see Tables 3.6a, 3.8.2, and 3.12.2.1.3 in the sponsor's safety update report and comparable tables in Dr. Oussova's review including table 11). For example, there were 7 CVA's (based on Dr. Oussova's adjudication of events; the sponsor reported 3 CVA's), 2 TIA's, and 12 MI's in the febuxostat group vs zero CVA/TIA and one MI in the allopurinol group in the randomized controlled studies (009, 010, and 004). In addition, there were 3 DVT/PE's in the febuxostat

group vs zero in the allopurinol group. In the (4 month) safety update report the numbers are 21 febuxostat vs 1 allopurinol for the combination endpoint of MI, stroke, TIA, and cardiac arrest.

Furthermore, there are a number of additional concerns. There were 8 cases of CHF in febuxostat vs one in allopurinol (again, in the controlled trials). There were 8 cases of SVT/a-fib in the febuxostat group vs 0 in allopurinol. There were 7 cases of pneumonia with febuxostat vs 0 with allopurinol; there were 4 cases of renal failure with febuxostat vs 0 with allopurinol. Even taking into account the differences in numbers exposed (randomization was usually in a 2:1 ratio between febuxostat and allopurinol and patient-years of exposure approaches 4 fold for febuxostat vs allopurinol), the rates of events in the febuxostat group appear to be greater than in the allopurinol treatment group.

There is one case of Guillan-Barre and one case of ITP in the febuxostat group. The significance of a single case of each is not known.

The numbers of discontinuations for skin related events is higher in the febuxostat group: 17 with 2 considered to be severe in intensity with febuxostat vs 2 events, both considered moderate in intensity, with allopurinol (see Table 3.5d in the original integrated summary of safety [ISS]). However, there were no cases of Stevens-Johnson, toxic epidermal necrolysis, or bullous rash reported in any group.

For liver related discontinuations, there were 28 with 2 severe (9 mild changes) in the febuxostat group vs 5 with zero severe (2 mild and 3 moderate changes) in the allopurinol group (see Table 3.6o in the original ISS; in the SUR there were 4 more cases on febuxostat). Two subjects in the febuxostat group developed ALT greater than or equal to 10X with concurrent total bilirubin greater than or equal to 2 mg/dL as compared to none in the allopurinol group. One of these subjects temporarily discontinued the drug but later resumed dosing and completed the study. There was one case of acute hepatitis (serious adverse event) in the febuxostat group vs 0 in the allopurinol group (there were a total of 4 liver related SAEs on febuxostat vs 1 on allopurinol; see Table 3.6n in the ISS).

Interestingly, there is also an increase in discontinuations for gouty flares. However, this may be an intrinsic property of a drug which has a potent urate lowering effect, and should not necessarily be viewed as a significant adverse event.

In summary, the totality of the safety profile for febuxostat is of concern. The overall mortality rate for febuxostat is higher than for allopurinol, even though there is no single cause of death that appears to stand out. Two cases of retroperitoneal hemorrhage in a data base of this size, is also disturbing (most likely related to changes in INR in patients on warfarin). Furthermore, in the context of the higher rate of CV related SAEs in the febuxostat group, the 2 deaths related to MIs are of greater concern. In addition to CV thromboembolic issues, there is an increase in SVT, and a higher rate of discontinuations due to skin and liver related events, some of which were labeled as severe, in the febuxostat group. These increases in event rates are not explained by differences in baseline covariates or concomitant medication use (such as NSAIDs), during

the trial. Although there are differences in numbers of patients exposed (patient-years of exposure; approximately 4 times higher in the febuxostat treatment group compared to allopurinol) in each of the treatment groups due to unbalanced randomization during the trials, the increased rate of events in the febuxostat group compared to the allopurinol (and placebo) treatment group exceed these differences. There is always a "risk" in post hoc pooling of events (the reviewer can pick and choose which events to combine) such as examining a collection of thromboembolic events, but the choice of MIs/strokes and cardiac deaths is one that has been used repeatedly for evaluating the CV Thromboembolic risks associated with the use of Cox-2 inhibitors. Since these studies are not powered to examine this endpoint, pooling is a reasonable solution to identifying signals in a data base of this size.

With so many AE associated with the use of febuxostat, there is some concern that this increase is "artificial", that is, related somehow to the imbalance in the numbers of subjects in the trials in the allopurinol vs febuxostat groups. On the face of it, it is difficult to identify a unifying mechanism that can account for all of these disparate events such as an increase in CV Thromboembolic events, pneumonias, as well as CHF, SVTs, and possibly other events. However, the onus is on the sponsor to provide additional data to address these safety issues.

1.3.4Dosing Regimen and Administration

The sponsor has adequately demonstrated the efficacy of the 80 and 120 mg doses. In addition the 240 mg dose demonstrated at least some increased efficacy over the 120 mg dose. However, the safety database for this dose is limited in both safety and efficacy, b(4)
However, only one phase II study examined the efficacy of the 40 mg dose. In this study 40 mg was clearly superior to placebo and although numerically less efficacious than the 80 mg dose, still appeared to provide acceptable efficacy. It is not clear why the applicant decided not to pursue this dose in the phase III trials. The applicant should be asked to study this dose (and possibly others) in additional trials to identify the lowest effective dose.

1.3.5Drug-Drug Interactions

Febuxostat will certainly be used in the same setting as colchicine and NSAIDs. Therefore, drug interaction studies with these drugs are critical. Some of these interactions are summarized below:

Colchicine
Administration of febuxostat with colchicine resulted in a slight increase in C_{max} (12%), but with no significant change in AUC of febuxostat. In addition, administration of colchicine with febuxostat did not have any significant effect on the C_{max} or AUC of colchicine. Therefore, no dose adjustment is necessary for febuxostat or colchicine when the two drugs are co-administered.

Indomethacin
Administration of febuxostat with indomethacin did not result in any significant changes in C_{max} or AUC of febuxostat or indomethacin. Therefore, no dose adjustment is necessary for febuxostat or indomethacin when the two drugs are co-administered.

Naproxen
Administration of febuxostat with naproxen resulted in a 28% increase in C_{max} and a 40% increase in AUC of febuxostat. The increases were not considered clinically significant. In addition, there were no significant changes in the C_{max} or AUC of naproxen. Therefore, no dose adjustment is necessary for febuxostat or naproxen when the two drugs are co-administered. For those taking naproxen with renal impairment, a dose reduction is recommended.

Patients who have elevated levels of serum urate will likely also be taking drugs such as diuretics and anticoagulants.

Hydrochlorothiazide
Administration of febuxostat with hydrochlorothiazide did not result in any significant changes in C_{max} or AUC of febuxostat. Serum uric acid concentrations were not substantially affected. Therefore, no dose adjustment is necessary for febuxostat when the two drugs are administered together.

Warfarin
Administration of warfarin with febuxostat did not result in any significant changes in C_{max} or AUC of warfarin. INR and Factor VII were not significantly affected by the co-administration offebuxostat . According to the sponsor no dose adjustment is necessary for warfarin when the two drugs are administered together. However, there were 2 cases of retroperitoneal hemorrhage resulting in death. Therefore, b(4)
at this time, until additional information about the interaction is obtained.

Azathioprine
However, drug interaction studies were not conducted with mercaptopurine or azathioprine although we know from the use of allopurinol and inhibition of XO, that this will result in an increase in mercaptopurine or azathioprine levels. On the basis of the mechanism of action of XO inhibition.

b(4)

The alternative would be to contraindicate the use of febuxostat in patients on any of these medications. This is the conservative approach.

Other
Finally, because glucuronidation is one of the major metabolism pathways for febuxostat, caution needs to be taken when coadminister febuxostat with a UGT inhibitor (e..g., diclofenac, probenecid, tacrolimus, cyclosporine) or inducer (e.g., rifampin).

1.3.6Special Populations

Renal Insufficiency
Following multiple doses of 80 mg of febuxostat in patients with mild, moderate or severe renal insufficiency, the C_{max} of febuxostat did not change, relative to subjects with normal renal function. The mean total AUC of febuxostat increased by approximately 1.8-fold from 7.5 μg·h/mL in the normal renal function group to 13.2 μg.h/mL in the severe renal function group. The C_{max} and AUC of active metabolites increased up to 2- and 4-fold, respectively. However, there were no clinically significant changes in the percent decrease in serum uric acid concentration (58% in normal renal function group and 55% in the severe renal function group). The sponsor comments that in subjects with severe renal impairment receiving febuxostat 80 mg daily for 7 days, the Cmax and AUC of the metabolites did not exceed those values in healthy subjects receiving 240 mg day for 14 days. The sponsor recommends that no dose adjustments are necessary for changes in renal function. b(4) see also the Clinical Pharmacology review by Dr. Zheng).

Hepatic Insufficiency
Following multiple doses of 80 mg of febuxostat in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, the C_{max} and AUC of febuxostat and its metabolites did not change significantly compared to subjects with normal hepatic function. Therefore, no dose adjustment appears necessary in patients with mild or moderate hepatic impairment. No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C), and caution should be exercised in those patients. Dose recommendations in severe hepatic impairment can not be made.

Geriatric
There were no significant changes observed in C_{max} or AUC of febuxostat or its metabolites following multiple oral doses of febuxostat in elderly patients as compared to younger patients. In addition, there were no clinically significant changes in the percent decrease in serum uric acid concentration. Therefore, no dose adjustment is necessary in elderly patients.

Pediatric
Febuxostat has not been investigated in patients <18 years of age.

Gender
Following multiple oral doses of febuxostat, the C_{max} and AUC were 24% and 12% higher in females than in males, respectively. However, weight-corrected C_{max} and AUC were similar between the genders. In addition, the difference between genders for percent decrease in serum uric acid concentrations was not clinically significant (59% in females vs. 52% in males). Therefore, no dose adjustment appears to be needed based on gender.

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

2. Introduction and Background

2.1Product Information

NDA 21-856 includes data to support marketing of the drug febuxostat (proposed trade name: Uloric) for the treatment of hyperuricemia associated with gout. This product is a new chemical entity. It is an oral tablet formulation in 80 and 120 mg doses to be used in adults with hyperuricemia associated with gout.

2.2Currently Available Treatment for Indications

Several alternatives to this product are available that lower serum uric acid and include such drugs as allopurinol (an alternate xanthine oxidase inhibitor), as well as uricosuric drugs such as probenecid and sulfinpyrazone. The uricosuric agents are effective for patients who have a relatively normal glomerular filtration rate (GFR) and who are willing to maintain a high fluid intake and good urine flow, and who have no history of nephrolithiasis. For all others, the drug of choice is allopurinol. Allopurinol hypersensitivity syndrome is a rare but serious toxicity with a high mortality rate. Oxypurinol, a metabolite of allopurinol is available for compassionate use only.

2.3Availability of Proposed Active Ingredient in the United States

This product is a new molecular entity and is not currently marketed in this country.

2.4Important Issues With Pharmacologically Related Products

The only other member of this pharmacologic class is allopurinol, another xanthine oxidase inhibitor. Dyspepsia, headache and diarrhea are the most common side effects of allopurinol. A pruritic papular rash occurs in 3-10% of patients. Additional toxicities include fever, urticaria, eosinophilia, interstitial nephritis, acute renal failure, bone marrow suppression, granulomatous hepatitis, vasculitis, and toxic epidermal necrolysis (TEN), as well as allopurinol hypersensitivity syndrome.

2.5Presubmission Regulatory Activity

The designs of the Phase 3 pivotal trials C02-009 (a 28-week Phase 3 trial) and C02-010 (a 52-week Phase 3 trial) were discussed with the Division at an End-of-Phase 2 meeting, and in subsequent teleconferences and correspondence. Agreement was reached with the Division on the study population (including subjects with high baseline serum urate levels), study design and

duration, control groups, doses of febuxostat and active comparator, the primary endpoint, clinical (secondary) endpoints, the criteria for demonstration of superiority to placebo, and the criteria for demonstration of non-inferiority and superiority to the active control in these trials. The acceptability of these trials to support the proposed indication was also discussed at the Pre-NDA meeting. In addition, the design of the pivotal trials and the endpoints used in these trials are consistent with the recommendations of the Arthritis Advisory Committee.

The selection of the design and doses for Study C02-023 to investigate the potential effect of febuxostat on cardiac repolarization, as assessed by the QTc interval, was also reviewed by the Division and found acceptable at the End-of-Phase 2 meeting.

In addition to the US studies, TAP's licensing partner, Teijin Pharma, conducted clinical studies with febuxostat within a Japan development program. As the Japan program evaluated lower doses of febuxostat (doses up to 50 mg QD) than those being developed in the US (80 mg QD and 120 mg QD) and a different demographic population, the submission of these studies as supportive for safety was also discussed.

2.6Other Relevant Background Information

This product is not approved in any foreign countries.

3. Significant Findings from Other Review Disciplines

3.1CMC (and Product Microbiology, if Applicable)

The reader is referred to the Chemistry review by Dr. Lin for a detailed review (this review has not been finalized at the time of this writing). From a chemistry review perspective, the NDA is approvable pending satisfactory response to the deficiencies in the dissolution method and acceptance criteria. The dissolution method and acceptance criterion remained unresolved at the time of completion of the chemistry review. Should a lower dosage strength be proposed for the drug product, the selection of medium (pH, paddle speed etc) should be revisited.

The chemistry reviewer had a number of labeling comments which are summarized below. For more details the reader is again referred to the chemistry review.

b(4)

3.2Animal Pharmacology/Toxicology

The following is excerpted from the pharmacology/toxicology review by Dr. Mukherjee (this review has not been finalized at the time of this writing; please also see the original review for labeling recommendations):

TMX-67 has no effect in the CNS, GI, cardiovascular and respiratory systems at pharmacodynamic doses. However, a transient hypotensive effect was observed in conscious beagle dogs at 5 and 50 mg/kg oral doses. TMX-67 showed a diuretic effect at 100 mg/kg single dose in rats associated with increased excretion of potassium, chloride and xanthine in the urine.

TMX-67 is rapidly absorbed after oral dosing and excreted as hydroxylated, carboxylated and desbutyl derivatives as Phase I metabolites in animals and humans. Glucuronidation of TMX-67 by Phase II metabolism (TMX-67 glucuronide) is the principle metabolite in human urine. The metabolic profiles were qualitatively similar in rodents, dogs and humans. Female mice showed a gender difference in the exposure. One of the hydroxylated metabolites (M1) of TMX-67 was formed by stereospecific enzyme activity in humans and rodents. Pharmacodynamic activity of the metabolites was not greater than TMX-67 for xanthine oxidase inhibition. Therefore, it is not considered to be a prodrug. P450 CYP1A1, CYP1A2 and CYP2C9 isozymes were involved in the Phase I metabolism. TMX-67 showed cross placental transfer and was excreted in the milk in rats. This resulted in deposition of xanthine crystals in the kidney of pups nursed by rats treated with TMX-67 at 48 mg/kg dose. Hepatic induction of enzyme was not evident from the studies.

It showed chromosomal aberration in Chinese hamster lung fibroblast cells in the presence and absence of S-9 liver homogenates in vitro.

TMX-67 showed papilloma and carcinoma of transitional cells in the urinary bladder in male F 344 rats at 24 mg/kg (16 times plasma exposure at maximum recommended human dose, MRHD). A similar effect was also noted in female B6C3F1 mice at 18.75 mg/kg (8 times human exposure). The neoplastic effect of TMX-67 was secondary to xanthine crystal deposition in the kidney and urinary bladder.

Reproductive safety studies did not show any effect for the fertility and reproductive performance. No teratogenicity, variation or embryocidal effect of TMX-67 was observed. However, nursing performance (F0) and survival of F1 generation were affected by the treatment with TMX-67 at 48 mg/kg in rats (25 times human plasma exposure at MRHD at MRHD). The excretion of drug through milk was also evident. Xanthine crystals were present in the kidney of neonatal rats delivered by dams treated with TMX-67 at 48 mg/kg.

Long term studies were conducted in rats and dogs to determine organ system toxicity and clinical signs. Salivation, diarrhea and vomiting were noted in beagle dogs. Salivation and decreased activity were noted in rats as clinical signs. A 12-month toxicity study in beagle dogs showed deposition of xanthine crystals and calculi in kidneys at 15 mg/kg (3.2 times human exposure at MRHD). A similar effect of calculus formation was noted in rats due to deposition of

xanthine crystals at 48 mg/kg (23 times human exposure at MRHD) in the six-month study. A similar effect was also observed in the 2-year rodent carcinogenicity studies.

Therefore, it is concluded that TMX-67 is a xanthine oxidase inhibitor. It is devoid of inhibitory activities in several enzymes involved in the DNA synthesis. TMX-67 was genotoxic in the chromosomal aberration assay. TMX-67 showed papilloma and carcinoma of transitional cell in the urinary bladder in rodents. The neoplastic changes were secondary to calculi formation in the kidney and urinary tract. It is not teratogenic and did not affect fertility and reproductive performance in rats. Major toxicity profile based on the non-clinical studies is increased xanthine deposition and formation of crystals in the kidney and urinary tract due to low solubility of xanthine (1 mg/15 ml of water). Therefore, the proposed clinical dose of 120 mg daily (2 mg/kg) is safe from the organ system toxicity based on the non-clinical studies. However, the possibility of calculus formation in the kidney and urinary tract could not be ruled out as it was observed in rats, mice and dogs following chronic treatment at doses that had 3.2-40 folds human exposure based on AUC at MRHD.

A. Pharmacologic activity:

TMX-67 is a non-purinergic inhibitor of xanthine oxidase in vitro with a K_i value of 10 nM. TMX-67 inhibited uric acid levels in the plasma at 1.6 and 5 mg/kg in rats and chimpanzee, respectively. It has negligible activity for the inhibition of purine and pyrimidine synthesis at the doses showed xanthine oxidase inhibitory activity. Therefore, it is not expected to have any anti-metabolite-like effect. The sponsor did not investigate its anti-inflammatory activity in appropriate models of experimental inflammation except urate crystal induced exudates formation in rats. However, the anti-inflammatory activity of TMX-67 could not be predicted from the results of the experiment. TMX-67 could show anti-inflammatory activity in hyperuricemia and associated clinical conditions due to xanthine oxidase inhibition. TMX-67 inhibited LPS induced TNF-α release in rats at 10 mg/kg/oral. Clinical significance of this effect is unknown

B. Non-clinical safety issues relevant to clinical use:

TMX-67 treatment would increase xanthine levels in the plasma and urine that may lead to form calculi in the kidney and urinary tract. Based on the non-clinical data, it is recommended that xanthine levels in the plasma and urine need to be monitored following chronic administration.

Reviewer's comments: From a clinical perspective, measuring xanthine levels will not provide useful clinical information.

4. Data Sources, Review Strategy, and Data Integrity

4.1Sources of Clinical Data

The sources of data used in this review include trials conducted by the applicant specifically for the marketing of this product. No postmarketing safety data or other sources of data were utilized.

4.2Tables of Clinical Studies

The following table summarizes the efficacy studies in the NDA. For a description of the studies used in the safety analysis, the reader is referred to the safety review by Dr. Oussova.

Table 1 : Febuxostat Efficacy Studies

Study	Treatment Groups	Design	N[a]	Duration of Treatment/ Duration of Gout Flare Prophylaxis During Treatment	Study Population	Primary Efficacy Endpoint
Phase 3 Pivotal Studies						
C02-009	Placebo Febuxostat: 80 mg QD 120 mg QD 240 mg QD Allopurinol: 300/100 mg QD[b]	Randomized, double-blind, parallel-group, active- and placebo-controlled	1072	28 weeks/ 8 weeks (naproxen or colchicine)	Male or female subjects between 18 and 85 years of age, inclusive, with hyperuricemia defined as a serum urate level ≥8.0 mg/dL on the Day -2 Visit; history or presence of gout defined by preliminary criteria of the ARA for the classification of the acute arthritis of primary gout.[109]	The proportion of subjects whose last 3 serum urate levels were <6.0 mg/dL.
C02-010	Febuxostat: 80 mg QD 120 mg QD Allopurinol: 300 mg QD	Randomized, double-blind, parallel-group, active-controlled	760	52 weeks/ 8 weeks (naproxen or colchicine)	Male or female subjects between 18 and 85 years of age, inclusive, with hyperuricemia defined as a serum urate level ≥8.0 mg/dL on the Day -2 Visit; history or presence of gout defined by preliminary criteria of the ARA for the classification of the acute arthritis of primary gout.[109]	The proportion of subjects whose last 3 serum urate levels were <6.0 mg/dL.
Supportive Phase 2 Controlled Study						
TMX-00-004	Placebo Febuxostat: 40 mg QD 80 mg QD 120 mg QD	Randomized, double-blind, parallel-group, placebo-controlled	153	4 weeks/ 2 weeks (colchicine)	Male or female subjects between 18 and 85 years of age, inclusive, with hyperuricemia defined as a serum urate level ≥8.0 mg/dL on the Day -2 Visit; history or presence of gout defined by preliminary criteria of the ARA for the classification of the acute arthritis of primary gout.[109]	The proportion of subjects whose serum urate level decreased to <6.0 mg/dL after treatment with study drug (Day 28).
Supportive Phase 3 Controlled Study						
C02-021[c]	Febuxostat: 80 mg QD 120 mg QD Allopurinol: 300/100 mg QD[c]	Randomized, open-label, active-controlled, safety extension	1074	Up to 24 months/ 8 weeks (naproxen or colchicine)	Subjects who completed Studies C02-009 or C02-010.	The proportion of subjects whose serum urate level decreased to <6.0 mg/dL.
Supportive Phase 2 Uncontrolled Study						
TMX-01-005[d]	Febuxostat: 40 mg QD 80 mg QD 120 mg QD	Open-label, safety extension	116	Up to 260 weeks/ 4 weeks (colchicine)	Subjects who completed Study TMX-00-004.	The proportion of subjects whose serum urate level decreased to or was maintained at <6.0 mg/dL.

ARA = American Rheumatism Association

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

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

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

d Ongoing study.

Cross-reference: ISE, Tables 8.1a and 8.1b

4.3Review Strategy

The 2 pivotal phase III trials were primarily used to establish efficacy. No literature was relied upon to support efficacy. For additional comments about the safety review, the reader is referred to the safety review by Dr. Oussova. For an integrated review of safety and efficacy, the reader is referred to the Executive summary found at the beginning of this document.

4.4Data Quality and Integrity

DSI was provided a list of approximately 10 sites from which to choose those to audit. Sites were selected based either on those investigators who recruited the most numbers of subjects, or the b(6)

The applicant also provided a debarment statement as follows: *TAP Pharmaceutical Products Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act, in connection with this Application.*

Allopurinol samples were obtained to assess the potency of comparator used in the 2 pivotal studies (see also clinical pharmacology review).

4.5Compliance with Good Clinical Practices

Trials were conducted in accordance with good clinical practices and according to acceptable ethical standards.

4.6Financial Disclosures

The applicant has adequately disclosed financial arrangements with clinical investigators. Only one investigator (Dr had any financial arrangements that might raise questions about the integrity of the data. However, this is unlikely to be a problem for 2 reasons. First, b(6)
. Second, the investigator recruited relatively few subjects in 2 large multi-site clinical trials , which is unlikely to influence the outcome of either trial.

5. Clinical Pharmacology

5.1Pharmacokinetics

The following section (*in italics*) is excerpted from the Clinical Pharmacology review:

From a Clinical Pharmacology and Biopharmaceutics point of view, the Sponsor has characterized the pharmacokinetic and pharmacodynamic performance of febuxostat. There are,

however, some areas of concern that need to be addressed:

1. The in vivo drug interaction potential of febuxostat with drugs that are xanthine oxidase (XO) substrates needs to be evaluated:
a. Theophylline: Febuxostat should be studied at its maximum proposed clinical dose and theophylline may be studied at a sub-therapeutic dose for decreasing side effects.
b. Mecaptopurine or azathioprine: Febuxostat should be studied at its maximum proposed clinical dose and mecaptopurine or azathioprine may be studied at a sub-therapeutic dose for decreasing side-effects.
The results of these studies will provide information on dose selection when these drugs are coadministered.
Without such studies, febuxostat needs to be contraindicated with theophylline, mecaptopurine and azathioprine.

2. The induction potential of febuxostat on human CYP-P450 needs to be evaluated. Such study could be conducted either in vitro (human hepatocytes) or in vivo. Based on the results to date, the sponsor may study induction potential on CYP3A and CYP1A first. If there is no induction on CYP3A, no further study to evaluate induction on CYP2C8 or CYP2C9 is needed. If there is induction on CYP3A, then they need to further study induction on CYP2C8 and CYP2C9.

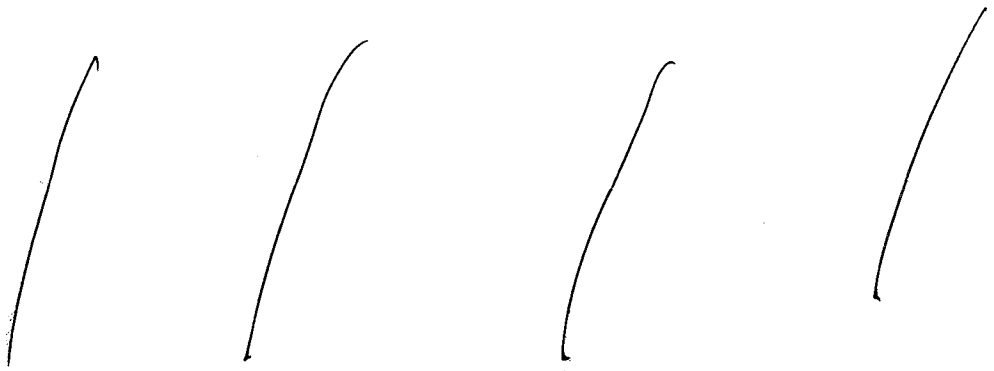
3. We do not agree with the Sponsor's conclusions as they relate an absence of a drug-drug interaction with warfarin. The removal of subjects with an increased INR in the warfarin drugdrug interaction trial lowered the strength of the results. We also note that there are reports of increased INR values in the clinical database in subjects on febuxostat, taken in conjunction b(4)

4. A review of the data presented in the NDA suggests that lower doses should be used in certain populations to maintain, on average, similar plasma levels with normal volunteers. b(4)

Please convey the following comments to the Sponsor regarding "dissolution method and acceptance criterion" for febuxostat 80 and 120 mg tablets:

1. Please test the dissolution of febuxostat 80 mg and 120 mg tablets using USP Apparatus 2 (paddle) at 75 rpm with 900 mL of 0.05 M potassium phosphate buffer, pH 6.8, maintained at 37°C with the following acceptance criterion:
Time Point ***Specification*** b(4)
15 minutes *Q =*
The current dissolution method and acceptance criterion will be revisited if lower dose strength tablets will be developed for future clinical studies. A different pH medium may be appropriate if solubility allows.

Labeling recommendations are deferred pending the completion of a successful clinical development program. The following items need to be considered at the time of future labeling:



b(4)

Additional clinical pharmacology information is presented below:

In healthy subjects, maximum plasma concentrations (C_{max}) and area under the plasma concentration time curve (AUC) of febuxostat increased in a dose proportional manner following single and multiple doses of 10 mg to 120 mg. For doses between 120 mg and 300 mg, a greater than dose proportional increase in AUC is observed for febuxostat. There is no appreciable accumulation when doses of 10 mg to 240 mg are administered every 24 hours. Febuxostat has an apparent mean terminal elimination half-life ($t_{1/2}$) of approximately 5 to 8 hours.

Population pharmacokinetic/pharmacodynamic analyses were conducted in 211 patients with hyperuricemia and gout, treated with FEBUXOSTAT 40-240 mg QD. Febuxostat pharmacokinetic parameters estimated by these analyses were similar to those estimated in healthy subjects.

Absorption
Febuxostat has a (t_{max} of 1.0-1.5 h) and is well absorbed (at least 84%). After single or multiple oral 80 and 120 mg once daily doses, C_{max} is approximately 2.8-3.2 μg/mL, and 5.0-5.3 μg/mL, respectively.

Following multiple oral 80 mg once daily doses or a single 120 mg dose with a high fat meal, there was a 49% and 38% decrease in C_{max} and a 18% and 16% decrease in AUC, respectively. However, no clinically significant change in the percent decrease in serum uric acid concentration was observed where tested (80 mg multiple dose). Thus, febuxostat may be taken without regard to food.

Concomitant ingestion of an antacid containing magnesium hydroxide and aluminum hydroxide has been shown to delay absorption of febuxostat (approximately 1 hour) and to cause a 32%

decrease in C_{max}, but no significant change in AUC was observed. Therefore, it appears that febuxostat may be taken without regard to antacid use.

Distribution
The apparent steady state volume of distribution (V_{ss}/F) of febuxostat ranges from 29 to 75 L after oral doses of 10-300 mg. The plasma protein binding of febuxostat is approximately 99.2%, (primarily to albumin), and is constant over the concentration range achieved with 80 and 120 mg doses.

Metabolism
Febuxostat is extensively metabolized by conjugation *via* uridine diphosphate glucuronosyltransferase (UGT) enzyme system and oxidation *via* cytochrome P450 (CYP) system. The oxidation of the isobutyl side chain leads to the formation of four pharmacologically active hydroxy metabolites, all of which occur in plasma of humans at a much lower extent than febuxostat. *In vitro* studies with human liver microsomes showed that those oxidative metabolites were formed primarily by CYP1A1, CYP1A2, CYP2C8 or CYP2C9 and febuxostat glucuronide was formed mainly by UGT 1A1, 1A8, and 1A9.

Excretion
Febuxostat is eliminated by both hepatic and renal pathways. Following an 80 mg oral dose of ^{14}C-labeled febuxostat, approximately 49% of the dose was recovered in the urine as unchanged febuxostat (3%), the acyl glucuronide of the drug (30%), its known oxidative metabolites and their conjugates (13%), and other unknown metabolites (3%). In addition to the urinary excretion, approximately 45% of the dose was recovered in the feces as the unchanged febuxostat (12%), the acyl glucuronide of the drug (1%), its known oxidative metabolites and their conjugates (25%), and other unknown metabolites (7%).

5.2Pharmacodynamics

Effect on Uric Acid and Xanthine Concentrations

In healthy subjects, febuxostat (10-300 mg QD) resulted in a decrease (approximately 27%-87%) in 24-hour mean serum uric acid concentrations, and an increase (approximately 1.5- to 10-fold from baseline) in 24-hour mean serum xanthine concentrations. In addition, there was a decrease in the total daily urinary uric acid excretion (approximately 40% to 93%). Also, there was a substantial increase in total daily urinary xanthine excretion (approximately 7- to 76-fold from baseline). There appeared to be a linear dose-response relationship in 24-hour mean serum uric acid concentrations at doses between 10 to 120 mg QD, which appeared to level off at doses above 120 mg QD. The 24-hour mean urinary xanthine concentration at 300 mg QD was 10.6 mg/dL. Urinary xanthine crystals have not been observed in clinical studies at doses of up to 300 mg QD. However, the development of xanthine stones needs to be further assessed after marketing because of the greater use (more patients for longer periods of time).

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

5.3Exposure-Response Relationships

The phase II and both phase III trials assessed dose response relationships. In all trials there was a clear dose response relationship in that the 120 mg dose demonstrated greater efficacy than the 80 mg dose which demonstrated greater efficacy than the 40 mg dose. The 240 mg dose was studied only in trial 009 and appeared to provide slightly greater efficacy than the 120 mg dose. In addition, the 240 mg dose appeared to be the only dose to reduce the number of gouty flares over the course of the 6 month trial. However, the sponsor has not proposed the 240 mg dose as a labeled dose. The sponsor should be requested to further study the 40 — mg doses for efficacy. b(5)

Evaluation of allopurinol encapsulated tablets:

The following is extracted (*in italics*) from the consult provided by the Division of Pharmaceutical Analysis (HFD-920; from B.J. Westenberger):

Background: *Febuxostat is a new treatment for hyperuricemia related to gout. During the clinical studies, the test product performed much better than the standard therapy, allopruinol. This increase in performance caused concern that the allopurinol tablets were either sub-potent or stored incorrectly which may have affected the drug release rate. Division of Pharmaceutical Analysis (DPA) was requested to perform quality assessment of four lots collected from —, — and to compare the results to the innovator's product, Zyloprim®.* b(4)

Conclusion: *Analyses of allopurinol encapsulated tablets collected from — — indicate that all products passed USP quality assessment tests thereby eliminating sub-potency or incorrect storage as possible reasons for differences observed during clinical studies.* b(4)

Experimental: *Color, shape, dimensions, and average tablet/capsule weight were recorded, as well as a digital photograph of each capsule and its contents. Uniformity of dosage, using the USP 28 assay method, was conducted on all samples. Chromatographic purity was assessed by using a technique known as High/Low chromatography based on the assay method. Dissolution profiles were determined using the USP 28 method with additional sampling times at 15, 30 and 60 minutes.*

Drug Product: *Zyloprim® (allopurinol) 300 mg Tablet, Lot 3G1974, EXP 10/07 (purchased by DPA)*

Allopurinol 300 mg Encapsulated Tablet, Lot 020145

Allopurinol 300 mg Encapsulated Tablet, Lot 020138
Allopurinol 300 mg Encapsulated Tablet, Lot 020065
Allopurinol 100 mg Encapsulated Tablet, Lot 020137

Results: *All samples met USP specifications for weight variation, uniformity of dosage, and % Dissolved in 45 minutes (See Tables 1 – 3). Chromatographic purity and dissolution profile data are in Tables 4 and 5. Dissolution profiles for all samples are presented in Figure 1. A representative photo of the broken tablet and contents of the 100mg capsule is presented in Figure 2. A representative photo of the broken tablet and contents of the 300mg capsule is presented in Figure 3. Microscopic examination of the powder in each capsule was identified as* ——— *Comparative evaluations of the four samples collected at* ——— *showed no difference between each other nor was any difference between these products and the purchased innovator product observed.* b(4)

6. Integrated Review of Efficacy

6.1Indication

The following indication is proposed for this product:

Febuxostat is indicated for the management of hyperuricemia in patients with gout.

Reviewers comments: the Division granted the claim for management of hyperuricemia and did not require that the sponsor demonstrate a reduction in the number of gout attacks. The literature supports this approach (and advisory committee deliberations also supported this approach) in that lowering uric acid to less than 6 is highly correlated with fewer gout attacks over the long term. Therefore the primary endpoint (see below) was the number of subjects with uric acid less than 6 mg/dL for the last 3 measures.

6.1.1Methods

There were 2 pivotal phase III efficacy trials used to support the indication sought by the sponsor. There was one phase II dose ranging study which provides supportive information. The 2 phase III trials are described in detail in the Appendix.

6.1.2General Discussion of Endpoints

The primary endpoint in both pivotal phase III trials was the number of subjects with a uric acid less than 6 mg/dL for the last 3 visits (subjects did not have to be completers, but only have their

last 3 serum urate levels available and less than 6). This was discussed with the sponsor and agreed to during previous negotiations. Furthermore, during an Arthritis Advisory Committee meeting, the committee agreed that the goal of uric acid lowering therapy was to lower the serum uric acid to less than 6 mg/dL (this leads to a negative urate balance). The literature supports this approach, and over the long term it is anticipated that this degree of urate lowering would lead to decreased complications from hyperuricemia such as recurrent gouty attacks.

However, in some sense, this has not been "validated" in prospective randomized controlled long term clinical trials, but rather, is based on (a considerable amount of) observational data in the literature. Never the less, this is the standard of care for individuals with hyperuricemia and gout, and appears to provide a reasonable assessment of clinical benefit. Again, it should be emphasized that this approach was supported by outside expert opinion provided at an Arthritis Advisory Committee meeting on this topic.

6.1.3 Study Design

Both pivotal phase III trials are considered adequate and well controlled studies to support the proposed indication. Both address the issue of blinding (overencapsulated drug products), randomization (use of IVRS and random generation of assignments), as well as a prospective statistical plan, and identification of endpoints.

In study 009 there was both a "positive" (allopurinol) and a "negative" (placebo) control. In study 010 only allopurinol was included as a control and utilized a non-inferiority design. Non-inferiority margins were pre-specified in the DAP.

Study 009 was 6 months long while study 010 was a year in length. Since both studies were only designed to examine the treatment of hyperuricemia, both are considered to be of adequate length to assess this endpoint. Neither was designed to formally address the issue of change in the number of gouty attacks, for example, although the data was collected and presented as a secondary analysis.

Entry criteria were similar between the 2 phase III trials and included subjects ranging in age from 18-85 with a history of gout as defined by American Rheumatism Association (ARA) criteria, with elevated serum urate levels (including subjects with levels above 10 mg/dL), and serum creatinine less than 2 mg/dL. Subjects intolerant of allopurinol were excluded because allopurinol was used as an active comparator in each study. However, this exclusion does not allow a determination of whether patients who do not respond to, or who cannot take allopurinol will respond to, or tolerate febuxostat (see Appendix for more details).

In the single phase II dose finding study, the sponsor examined doses ranging from 40 mg to 120 mg including doses of 80, 120 that were further studied in the phase III trials. The sponsor will recommend the 80 and 120 mg doses as the appropriate doses for clinical practice. However, based on the phase II trial the 40 mg dose may be efficacious. The 240 mg dose was studied for

efficacy (in one phase III trial) but not adequately for safety purposes. However, the 240 mg dose appeared to provide the most convincing evidence of reduction in numbers of gouty attacks. The sponsor should be encouraged to study — the 40 mg [redacted] b(4)

6.1.4 Efficacy Findings

Please refer to Section 10.1 (Appendix) for a detailed discussion of each trial. An integrated summary of results will be presented in this section.

The primary outcome measure in both trials was the number of subjects with serum urate level less than 6 mg/dL for the last 3 visits (subjects did not have to complete the entire study as long as their last 3 serum urate levels were available and less than 6). The next table summarizes the results of both pivotal trials for the primary endpoint.

Primary endpoint

Table 2 : Proportion of Subjects Whose Last 3 Serum Urate Levels Were<6.0 mg/dL - ITT Subjects (Phase 3 Pivotal Studies)

Last 3 Serum Urate Levels <6.0 mg/dL	Placebo n/N (%)	Febuxostat 80 mg QD n/N (%)	Febuxostat 120 mg QD n/N (%)	Febuxostat 240 mg QD n/N (%)	Allopurinol 300/100 mg QD n/N (%)
Yes	0/134 (0%)	262/517 (51%)[m]	329/519 (63%)	92/134 (69%)	113/519 (22%)
No	134/134 (100%)	255/517 (49%)	190/519 (37%)	42/134 (31%)	406/519 (78%)

	Difference in Proportions	97.5% CI†	P-value‡
Febuxostat 80 mg vs. Allopurinol 300/100 mg	29%	(22.5%, 35.3%)	<0.001#
Febuxostat 120 mg vs. Allopurinol 300/100 mg	42%	(35.4%, 47.9%)	<0.001#

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

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

‡ P-values from a CMH test stratified by study.

Statistically significant difference versus allopurinol 300/100 mg QD (p≤0.05) using Hochberg's procedure for multiple comparisons.

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

Cross-reference: Module 5.3.5.3.1, Statistical Table 3.2.1.1

Reviewers comments: there is a modest dose response suggesting that the 240 mg dose may provide greater efficacy than the 120 mg dose. It is possible that those subject who do not reach a serum urate level less than 6 on 120 may benefit from a higher dose. However, safety at the 240 mg dose is limited. The sponsor does not propose that the 240 mg dose be labeled.

Because a subject did not have to complete the study to be considered a responder, an example of a completer analysis for one of the trials, trial 009, is shown in the next table. This analysis is consistent with the original analysis based on the last 3 measurements.

Table 3: completers

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

	Placebo	Febuxostat 80 mg QD	Febuxostat 120 mg QD	Febuxostat 240 mg QD	Allopurinol 300/100 mg QD
Last 3 Serum Urate < 6.0 mg/dL					
Yes	0.0% (0/101)	58.0% (96/169)	74.0% (148/200)	83.7% (72/ 86)	27.0% (57/211)
No	100.0% (101/101)	42.0% (71/169)	26.0% (52/200)	16.3% (14/ 86)	73.0% (154/211)
		Difference in Proportions	97.5% CI (a)	P-values (b)	
Primary Comparisons					
Febux 80 mg vs Allo 300/100 mg		31.0%	(20.0%, 41.9%)	<0.001#	
Febux 120 mg vs Allo 300/100 mg		47.0%	(37.2%, 56.7%)	<0.001#	
Additional Comparisons					
Febux 80 mg vs Placebo				<0.001##	
Febux 120 mg vs Placebo				<0.001##	
Febux 240 mg vs Placebo				<0.001##	
Febux 240 mg vs Allo 300/100 mg				<0.001***	
Allo 300/100 mg vs Placebo				<0.001***	
Febux 80 mg vs Febux 120 mg				0.001***	
Febux 80 mg vs Febux 240 mg				<0.001***	
Febux 120 mg vs Febux 240 mg				0.004	

(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.

The goal of lowering serum urate levels is to keep the level less than 6 in order to ensure a negative urate balance and ultimately reduce the body urate load. Therefore, the sponsor was requested to provide additional analyses shown in the next 2 tables. The first is an analysis of subjects with all serum urate levels less than 6 after the first 4 weeks of the study, for trial 009, as an example. This is a high bar but readily demonstrates the efficacy of febuxostat compared to allopurinol. The second table is a completer analysis for the same endpoint.

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Table 4 : all serum urate levels less than 6 mg/dL

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

	Placebo	Febuxostat 80 mg QD	Febuxostat 120 mg QD	Febuxostat 240 mg QD	Allopurinol 300/100 mg QD
All Serum Urate < 6.0 mg/dL					
Yes	0.0% (0/120)	46.2% (107/231)	60.9% (151/248)	73.9% (85/115)	18.1% (44/243)
No	100.0% (120/120)	53.7% (124/231)	39.1% (97/248)	26.1% (30/115)	81.9% (199/243)
		Difference in Proportions	97.5% CI (a)	P-values (b)	
Primary Comparisons					
Febux 80 mg vs Allo 300/100 mg		28.2%	(19.9%, 37.4%)	<0.001#	
Febux 120 mg vs Allo 300/100 mg		42.8%	(33.0%, 51.7%)	<0.001#	
Additional Comparisons					
Febux 80 mg vs Placebo				<0.001##	
Febux 120 mg vs Placebo				<0.001##	
Febux 240 mg vs Placebo				<0.001##	
Febux 240 mg vs Allo 300/100 mg				<0.001***	
Allo 300/100 mg vs Placebo				<0.001***	
Febux 80 mg vs Febux 120 mg				0.001***	
Febux 80 mg vs Febux 240 mg				<0.001***	
Febux 120 mg vs Febux 240 mg				0.017*	

Success subjects are defined as serum urate < 6.0 mg/dL for every visit on week 4 or later.
The denominator for each treatment group is the number of subjects with at least one visit on week 4 or later.
(a) 97.5% confidence interval for the difference in proportions based on the normal approximation for the binomial distribution.
(b) P-values are from a Cochran-Mantel-Haenszel test stratified by baseline renal function (serum creatinine<=1.5 vs >1.5 mg/dL).
# Indicates statistical significance at the 0.05 level versus 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.

Table 5: completers

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

	Placebo	Febuxostat 80 mg QD	Febuxostat 120 mg QD	Febuxostat 240 mg QD	Allopurinol 300/100 mg QD
All Serum Urate < 6.0 mg/dL					
Yes	0.0% (0/101)	46.7% (79/169)	63.0% (126/200)	73.1% (63/ 86)	17.5% (37/211)
No	100.0% (101/101)	53.3% (90/169)	37.0% (74/200)	26.7% (23/ 86)	82.5% (174/211)
		Difference in Proportions	97.5% CI (a)	P-values (b)	
Primary Comparisons					
Febux 80 mg vs Allo 300/100 mg		29.2%	(18.9%, 39.0%)	<0.001#	
Febux 120 mg vs Allo 300/100 mg		44.5%	(34.6%, 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				0.004**	
Febux 80 mg vs Febux 240 mg				<0.001***	
Febux 120 mg vs Febux 240 mg				0.077	

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

In all of the above analyses, the 240 mg dose appears to demonstrate greater efficacy than the 120 mg dose. b(4)

A number of secondary endpoints were examined by the sponsor, and pooled data for the 2 pivotal studies is provided below.

Table 6: Proportion of Subjects with Serum Urate Levels <6.0 mg/dL, <5.0 mg/dL, and <4.0 mg/dL at the Week 28, Week 52, and Final Visits - ITT Subjects (Phase 3 Pivotal Studies)

Visit	Placebo n/N	Placebo (%)	Febuxostat 80 mg QD n/N	Febuxostat 80 mg QD (%)	Febuxostat 120 mg QD n/N	Febuxostat 120 mg QD (%)	Febuxostat 240 mg QD n/N	Febuxostat 240 mg QD (%)	Allopurinol 300/100 mg QD n/N	Allopurinol 300/100 mg QD (%)
<6.0 mg/dL										
Week 28	1/99	(1%)	255/347	(73%)[a,m]	293/347	(84%)[a]	78/83	(94%)	169/407	(42%)
Week 52	--	--	129/159	(81%)[a]	119/145	(82%)[a]	--	--	70/178	(39%)
Final	1/127	(1%)	368/502	(73%)[a,m]	402/507	(79%)[a]	116/126	(92%)	190/505	(38%)
<5.0 mg/dL										
Week 28	0/99	(0%)	175/347	(50%)[a,m]	243/347	(70%)[a]	72/83	(87%)	48/407	(12%)
Week 52	--	--	87/159	(55%)[a,m]	103/145	(71%)[a]	--	--	26/178	(15%)
Final	0/127	(0%)	234/502	(47%)[a,m]	331/507	(65%)[a]	106/126	(84%)	65/505	(13%)
<4.0 mg/dL										
Week 28	0/99	(0%)	73/347	(21%)[a,m]	148/347	(43%)[a]	65/83	(78%)	7/407	(2%)
Week 52	--	--	36/159	(23%)[a,m]	65/145	(45%)[a]	--	--	3/178	(2%)
Final	0/127	(0%)	96/502	(19%)[a,m]	200/507	(39%)[a]	95/126	(75%)	10/505	(2%)

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

Note: Study C02-009 was a 28-week trial that included placebo and febuxostat 240 mg QD treatment groups. Thus, there are no Week 52 data for these 2 groups of subjects.

a Statistically significant difference versus allopurinol 300/100 mg QD ($p \leq 0.05$) using a CMH test stratified by study.

m Statistically significant difference versus febuxostat 120 mg QD ($p \leq 0.05$) using a CMH test stratified by study.

Cross-reference: Module 5.3.5.3.1, Statistical Tables 3.2.2.1, 3.2.2.3, and 3.2.2.4

Reviewers comments: the pooled data supports the efficacy of febuxostat compared to allopurinol in driving the serum urate to less than even 4 mg/dL.

Table 7 : Proportion of Subjects with Serum Urate Level <6.0 mg/dL at the Final Visit by Baseline Serum Urate - ITT Subjects (Phase 3 Pivotal Studies)

Baseline Serum Urate	Placebo		Febuxostat 80 mg QD		Febuxostat 120 mg QD		Febuxostat 240 mg QD		Allopurinol 300/100 mg QD	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
<9.0 (mg/dL)	1/32	(3%)	114/132	(86%)[a]	124/141	(88%)[a]	30/31	(97%)	79/140	(56%)
9.0 - <10.0 (mg/dL)	0/50	(0%)	122/163	(75%)[a,m]	139/157	(89%)[a]	43/46	(93%)	70/173	(40%)
≥10.0 (mg/dL)	0/45	(0%)	132/207	(64%)[a]	139/209	(67%)[a]	43/49	(88%)	41/192	(21%)

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

Note: Baseline for Study C02-009 was defined as the average of the serum urate measurements within the baseline window (Days -10 to 1). If a subject had more than 3 measurements within the baseline window, the last 3 measurements were used. Baseline for Study C02-010 was defined as the average of the Day -2 and Day 1 serum urate measurements.

a Statistically significant difference versus allopurinol 300/100 mg QD ($p<0.05$) using a CMH test stratified by study.

m Statistically significant difference versus febuxostat 120 mg QD ($p\leq0.05$) using a CMH test stratified by study.

Cross-reference: Module 5.3.5.3.1, Statistical Table 3.2.2.2

Reviewers comments: even at higher baseline serum urate levels, febuxostat is superior to allopurinol. Again there appears to be dose response for febuxostat even up to the 240 mg dose.

Table 8: Mean Percent Change from Baseline in Serum Urate Levels at the Week 28, Week 52, and Final Visits - ITT Subjects (Phase 3 Pivotal Studies)

	Placebo		Febuxostat 80 mg QD		Febuxostat 120 mg QD		Febuxostat 240 mg QD		Allopurinol 300/100 mg QD	
Visit	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Actual Value (mg/dL)										
Baseline Mean	134	9.80 (1.367)	517	9.88 (1.290)	519	9.86 (1.244)	134	9.81 (1.191)	519	9.84 (1.223)
Week 28	99	9.25 (1.544)	347	5.20 (1.634)	347	4.47 (1.644)	83	3.18 (1.897)	407	6.37 (1.438)
Week 52	--	--	159	5.07 (1.682)	145	4.64 (2.095)	--	--	178	6.37 (1.453)
Final	127	9.45 (1.611)	502	5.40 (1.882)	507	4.77 (2.028)	126	3.32 (2.080)	505	6.53 (1.595)
Percent Change from Baseline (%)										
Week 28	99	-3.58 (13.846)	347	-46.88[a,m] (15.797)	347	-54.26[a] (16.517)	83	-67.83 (18.182)	407	-34.56 (13.579)
Week 52	--	--	159	-47.74[a,m] (17.502)	145	-53.02[a] (19.312)	--	--	178	-34.75 (13.560)
Final	127	-2.99 (13.283)	502	-44.98[a,m] (18.614)	507	-51.71[a] (18.913)	126	-66.32 (20.616)	505	-33.36 (15.017)

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

Note: Baseline for Study C02-009 was defined as the average of the serum urate measurements within the baseline window (Days -10 to 1). If a subject had more than 3 measurements within the baseline window, the last 3 measurements were used. Baseline for Study C02-010 was defined as the average of the Day -2 and Day 1 serum urate measurements. Study C02-009 was a 28-week trial that included placebo and febuxostat 240 mg QD treatment groups. Thus, there are no Week 52 data for these 2 groups of subjects.

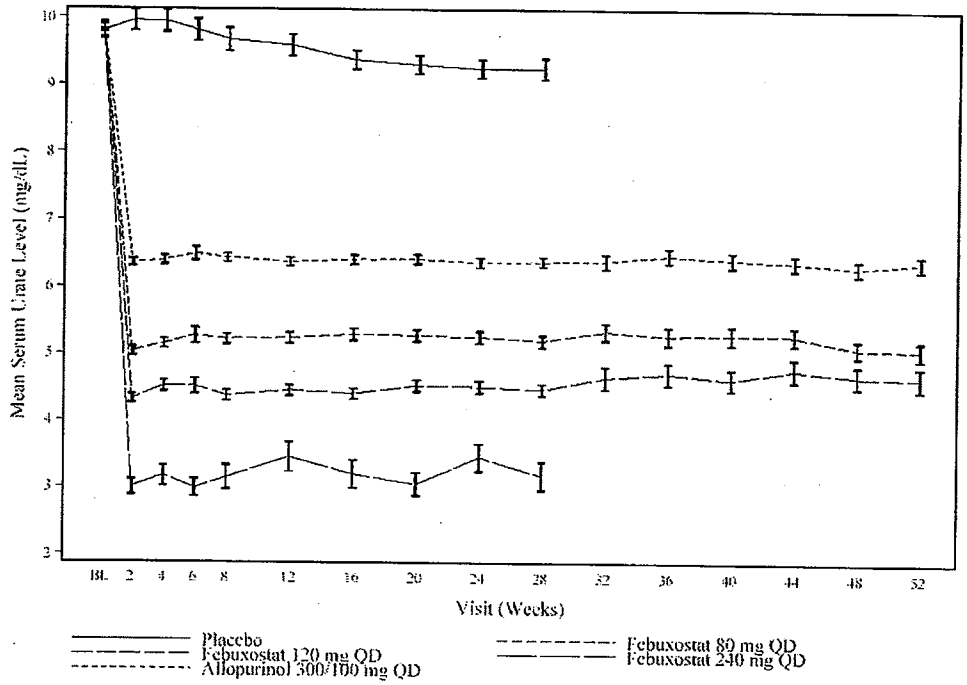
a Statistically significant difference versus allopurinol 300/100 mg QD ($p \leq 0.05$) using ANOVA with treatment and study as factors.

m Statistically significant difference versus febuxostat 120 mg QD ($p \leq 0.05$) using ANOVA with treatment and study as factors.

Cross-reference: Module 5.3.5.3.1, Statistical Table 3.2.2.5

Reviewers comments: although the baseline serum urate levels are similar, the percent change is greatest in the febuxostat treatment groups even compared to allopurinol. There is a clear dose response suggesting that the 240 mg dose may provide more efficacy than the 120 mg dose.

Figure 1: Mean (±SEM) Serum Urate Levels by Visit - ITT Subjects (Phase 3 Pivotal Studies)



SEM = Standard error of the mean.

Phase 3 pivotal studies included: C02-009 and C02-010.
Statistical Figure 3.2.2.5.1

Reviewers comments: this graph provides a visual representation of a dose response over the course of 52 weeks. It appears that once lowered, the serum urate level remains relatively consistent.

Table 9: Median and Mean Percent Change from Baseline in Primary Tophus Size at the Week 28, Week 52, and Final Visits - ITT Subjects with a Primary Palpable Tophus at Baseline (Phase 3 Pivotal Studies)

Visit	Placebo			Febuxostat 80 mg QD			Febuxostat 120 mg QD			Febuxostat 240 mg QD			Allopurinol 300/100 mg QD		
	N	Median (25^{th} p., 75^{th} p.)	Mean	N	Median (25^{th} p., 75^{th} p.)	Mean	N	Median (25^{th} p., 75^{th} p.)	Mean	N	Median (25^{th} p., 75^{th} p.)	Mean	N	Median (25^{th} p., 75^{th} p.)	Mean
Actual Value (mm^2)															
Baseline	29	840.0 (300.0, 2310.0)	1547.8	98	806.0 (323.0, 2209.0)	1898.3	106	636.0 (270.0, 1900.0)	1667.3	25	650.0 (340.0, 1764.0)	1376.7	109	625.0 (300.0, 1575.0)	1400.7
Week 28	21	400.0 (144.0, 1000.0)	958.2	62	554.5 (120.0, 1520.0)	1250.5	63	200.0 (12.0, 75.0)	836.6	14	150.0 (36.0, 625.0)	519.3	79	340.0 (100.0, 899.0)	818.0
Week 52	--	--	--	32	186.0 (0.0, 935.0)	517.0	26	289.5 (64.0, 864.0)	527.3	--	--	--	30	272.5 (100.0, 1482.0)	991.6
Final	26	387.5 (121.0, 1000.0)	853.2	92	445.0 (3.0, 1287.5)	957.5	101	323.0 (40.0, 1200.0)	1309.5	24	280.0 (54.0, 855.0)	666.3	105	320.0 (100.0, 1184.0)	1036.0
Percent Change from Baseline (%)															
Week 28	21	-52.0 (-62.5, -21.4)	-33.6	62	-34.7[m] (-79.3, 3.0)	27.7	63	-52.7[a] (-90.3, -26.2)	-49.7	14	-53.2 (-77.8, -22.1)	-52.7	79	-28.6 (-68.8, 0.0)	-20.3
Week 52	--	--	--	32	-83.4 (-100.0, -15.6)	936.0	26	-65.5 (-85.5, -38.9)	-56.3	--	--	--	30	-49.7 (-96.0, 0.0)	-26.7
Final	26	-40.3 (-62.5, -16.7)	-33.7	92	-43.9 (-98.7, 0.0)	310.8	101	-43.8 (-84.9, 0.0)	-28.3	24	-47.0 (-80.0, -13.8)	-41.4	105	-25.0 (-66.9, 0.0)	-18.3

Phase 3 pivotal studies included: C02-009 and C02-010.
Note: Baseline was defined as the last examination prior to the first dose of study drug. Study C02-009 was a 28-week trial that included placebo and febuxostat 240 mg QD treatment groups. Thus, there are no Week 52 data for these 2 groups of subjects.
25^{th} p. = 25^{th} percentile; 75^{th} p. = 75^{th} percentile
a Statistically significant difference in percent change values versus allopurinol 300/100 mg QD ($p \leq 0.05$) using the Wilcoxon rank-sum test.
m Statistically significant difference in percent change values versus febuxostat 120 mg QD ($p \leq 0.05$) using the Wilcoxon rank-sum test.
Cross-reference: Module 5.3.5.3.1, Statistical Table 3.2.2.6

Reviewers comments: there is a wide variation in the size of tophi. However, the changes appear to be greatest for febuxostat although the percent change shows little dose response. The accuracy and reproducibility of these measurements is questionable.

Table 10: Median and Mean Percent Change from Baseline in Primary Tophus Size by Average Post-baseline Serum Urate Level at the Week 28, Week 52, and Final Visits - ITT Subjects with a Primary Palpable Tophus at Baseline (Phase 3 Pivotal Studies)

Visit	Serum Urate <6.0 mg/dL			Serum Urate ≥6.0 mg/dL		
	N	Median (25^{th} p., 75^{th} p.)	Mean	N	Median (25^{th} p., 75^{th} p.)	Mean
Actual Value (mm^2)						
Baseline	196	625.0 (262.5, 1600.0)	1306.5	155	900.0 (320.0, 2430.0)	1940.0
Week 28	138	240.0 (15.0, 750.0)	685.3	101	500.0 (130.0, 1400.0)	1260.0
Week 52	54	181.5 (0.0, 864.0)	498.1	34	448.0 (120.0, 1225.0)	973.1
Final	193	225.0 (2.0, 864.0)	694.8	149	484.0 (121.0, 1400.0)	1431.9
Percent Change from Baseline (%)						
Week 28	138	-48.2† (-87.2, -14.1)	-17.7	101	-30.6 (-62.5, 0.0)	-20.1
Week 52	54	-75.0 (-100.0, -31.8)	540.0	34	-49.7 (-81.9, -7.4)	-43.3
Final	193	-51.3† (-99.7, -7.7)	124.6	149	-24.2 (-59.5, 0.0)	-15.1

Phase 3 pivotal studies included: C02-009 and C02-010.
Note: Baseline was defined as the last examination prior to the first dose of study drug.
25^{th} p. = 25^{th} percentile; 75^{th} p. = 75^{th} percentile
† Statistically significant difference in percent change values versus subjects with average post-baseline serum urate ≥6.0 mg/dL ($p \leq 0.05$) using the Wilcoxon rank-sum test.
Cross-reference: Module 5.3.5.3.1, Statistical Tables 3.2.2.9, 3.2.2.10, and 3.2.2.11

Table 11: Subjects Requiring Treatment for a Gout Flare by Time Interval - ITT Subjects (Phase 3 Pivotal Studies)

Time Interval	Placebo n/N	Placebo (%)	Febuxostat 80 mg QD n/N	Febuxostat 80 mg QD (%)	Febuxostat 120 mg QD n/N	Febuxostat 120 mg QD (%)	Febuxostat 240 mg QD n/N	Febuxostat 240 mg QD (%)	Allopurinol 300/100 mg QD n/N	Allopurinol 300/100 mg QD (%)
Screening	12/134	(9%)	41/517	(8%)	56/519	(11%)	13/134	(10%)	40/519	(8%)
Day 1 to Week 52	74/134	(55%)	312/517	(60%)[m]	348/519	(67%)[a]	89/134	(66%)	299/519	(58%)
Day 1 to Week 8	27/134	(20%)	128/517	(25%)[m]	187/519	(36%)[a]	61/134	(46%)	113/519	(22%)
Week 8 to Week 52	62/119	(52%)	268/451	(59%)	279/455	(61%)[a]	60/106	(57%)	260/471	(55%)
Week 8 to Week 12	34/118	(29%)	159/451	(35%)	188/455	(41%)	45/106	(42%)	137/471	(29%)
Week 12 to Week 16	23/112	(21%)	118/424	(28%)	99/426	(23%)	15/ 99	(15%)	104/455	(23%)
Week 16 to Week 20	23/107	(21%)	86/402	(21%)	89/409	(22%)	8/94	(9%)	82/436	(19%)
Week 20 to Week 24	17/104	(16%)	68/384	(18%)	66/388	(17%)	12/91	(13%)	68/426	(16%)
Week 24 to Week 28	18/103	(17%)	52/369	(14%)	64/380	(17%)	6/89	(7%)	59/421	(14%)
Week 28 to Week 32	4/50	(8%)	40/276	(14%)	22/276	(8%)	1/39	(3%)	37/310	(12%)
Week 32 to Week 36	--	--	24/190	(13%)	24/167	(14%)	--	--	25/199	(13%)
Week 36 to Week 40	--	--	23/181	(13%)	12/163	(7%)	--	--	24/194	(12%)
Week 40 to Week 44	--	--	18/177	(10%)	17/161	(11%)	--	--	22/191	(12%)
Week 44 to Week 48	--	--	16/170	(9%)	11/157	(7%)	--	--	20/189	(11%)
Week 48 to Week 52	--	--	13/167	(8%)	9/153	(6%)	--	--	19/185	(10%)

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

Note: The numerator is the number of subjects requiring treatment for a gout flare in the time interval and treatment group being summarized. The denominator is the number of subjects exposed to at least 1 dose of that treatment in the time interval being summarized.
Study C02-009 was a 28-week trial that included placebo and febuxostat 240 mg QD treatment groups. Thus, there are no data after the Week 28 to 32 time interval for these 2 groups of subjects.

a Statistically significant difference versus allopurinol 300/100 mg QD ($p \leq 0.05$) using a CMH test stratified by study.

m Statistically significant difference versus febuxostat 120 mg QD ($p \leq 0.05$) using a CMH test stratified by study.

Cross-reference: Module 5.3.5.3.1, Statistical Table 3.2.2.18

Reviewers comments: Neither trial was designed to adequately assess the incidence of gouty flares. The percent of subjects with flares at the end of the placebo period is similar to those in the treated groups, at both the 28-32 week period and at the 48-52 week period. Therefore, robust evidence of a decrease in gouty attacks with febuxostat treatment has not been provided.

A number of additional analyses of gouty flares are provided in the next series of tables. Because the overall incidence of flares in the above table was not different between the groups, these sensitivity analyses should be viewed as hypothesis generating and do not provide robust evidence of efficacy.

Table 12 : Subjects Requiring Treatment for a Gout Flare by Time Interval and Average Post-baseline Serum Urate Level - ITT Subjects (Phase 3 Pivotal Studies)

Time Interval	Serum Urate <6.0 mg/dL		Serum Urate ≥6.0 mg/dL	
	n/N	(%)	n/N	(%)
Screening	103/1126	(9%)	57/641	(9%)
Day 1 to Week 52	729/1126	(65%)	385/641	(60%)
Day 1 to Week 8	337/1126	(30%)	171/641	(27%)
Week 8 to Week 52	602/1022	(59%)	327/580	(56%)
Week 8 to Week 12	387/1022	(38%)	176/579	(30%)
Week 12 to Week 16	232/972	(24%)	127/544	(23%)
Week 16 to Week 20	186/930	(20%)	102/518	(20%)
Week 20 to Week 24	141/893	(16%)	90/500	(18%)
Week 24 to Week 28	117/874	(13%)	82/488	(17%)
Week 28 to Week 32	56/618	(9%)	48/333	(14%)
Week 32 to Week 36	49/380	(13%)	24/176	(14%)
Week 36 to Week 40	32/368	(9%)	27/170	(16%)
Week 40 to Week 44	34/362	(9%)	23/167	(14%)
Week 44 to Week 48	25/354	(7%)	22/162	(14%)
Week 48 to Week 52	20/346	(6%)†	21/159	(13%)

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

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

† Statistically significant difference versus subjects with average post-baseline serum urate ≥6.0 mg/dL ($p \leq 0.05$) using a CMH test stratified by study.

Cross-reference: Module 5.3.5.3.1, Statistical Tables 3.2.2.19, 3.2.2.20, and 3.2.2.21

Table 13 : Subjects Requiring Treatment for a Gout Flare by Time Interval - ITT Subjects with an Average Post-baseline Serum Urate Level <6.0 mg/dL (Phase 3 Pivotal Studies)

Time Interval	Placebo		Febuxostat 80 mg QD		Febuxostat 120 mg QD		Febuxostat 240 mg QD		Allopurinol 300/100 mg QD	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
Screening	0/0	--	29/374	(8%)	48/443	(11%)	13/120	(11%)	13/189	(7%)
Day 1 to Week 52	0/0	--	236/374	(63%)	304/443	(69%)	86/120	(72%)	103/189	(54%)
Day 1 to Week 8	0/0	--	90/374	(24%)	157/443	(35%)	59/120	(49%)	31/189	(16%)
Week 8 to Week 52	0/0	--	204/339	(60%)	247/405	(61%)	59/100	(59%)	92/178	(52%)
Week 8 to Week 12	0/0	--	122/339	(36%)	170/405	(42%)	45/100	(45%)	50/178	(28%)
Week 12 to Week 16	0/0	--	95/324	(29%)	88/381	(23%)	15/93	(16%)	34/174	(20%)
Week 16 to Week 20	0/0	--	70/305	(23%)	77/367	(21%)	8/88	(9%)	31/170	(18%)
Week 20 to Week 24	0/0	--	53/293	(18%)	55/347	(16%)	11/86	(13%)	22/167	(13%)
Week 24 to Week 28	0/0	--	36/283	(13%)	55/341	(16%)	6/85	(7%)	20/165	(12%)
Week 28 to Week 32	--	--	30/215	(14%)	18/249	(7%)	1/37	(3%)	7/117	(6%)
Week 32 to Week 36	--	--	18/150	(12%)	21/149	(14%)	--	--	10/81	(12%)
Week 36 to Week 40	--	--	16/142	(11%)	11/145	(8%)	--	--	5/81	(6%)
Week 40 to Week 44	--	--	15/138	(11%)	13/143	(9%)	--	--	6/81	(7%)
Week 44 to Week 48	--	--	10/133	(8%)	9/140	(6%)	--	--	6/81	(7%)
Week 48 to Week 52	--	--	9/131	(7%)	6/136	(4%)	--	--	5/79	(6%)

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

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

Study C02-009 was a 28-week trial that included placebo and febuxostat 240 mg QD treatment groups. Thus, there are no data after the Week 28 to 32 time interval for these 2 groups of subjects.

Cross-reference: Module 5.3.5.3.1, Statistical Table 3.2.2.19

Table 14 : Subjects Requiring Treatment for a Gout Flare by Time Interval - ITT Subjects with Tophus Present at Baseline (Phase 3 Pivotal Studies)

	Placebo		Febuxostat 80 mg QD		Febuxostat 120 mg QD		Febuxostat 240 mg QD		Allopurinol 300/100 mg QD	
Time Interval	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
Screening	3/30	(10%)	9/99	(9%)	14/111	(13%)	3/26	(12%)	12/113	(11%)
Day 1 to Week 52	20/30	(67%)	68/99	(69%)	84/111	(76%)	19/26	(73%)	73/113	(65%)
Day 1 to Week 8	9/30	(30%)	24/99	(24%)[m]	51/111	(46%)[a]	12/26	(46%)	34/113	(30%)
Week 8 to Week 52	18/24	(75%)	60/83	(72%)	68/87	(78%)[a]	14/22	(64%)	61/100	(61%)
Week 8 to Week 12	10/24	(42%)	38/83	(46%)	50/87	(57%)	12/22	(55%)	32/100	(32%)
Week 12 to Week 16	10/24	(42%)	29/77	(38%)	30/83	(36%)	5/21	(24%)	28/92	(30%)
Week 16 to Week 20	6/24	(25%)	25/73	(34%)	24/77	(31%)	2/20	(10%)	20/89	(22%)
Week 20 to Week 24	6/23	(26%)	19/71	(27%)	21/72	(29%)	1/19	(5%)	17/85	(20%)
Week 24 to Week 28	4/22	(18%)	14/70	(20%)	19/71	(27%)	1/18	(6%)	15/85	(18%)
Week 28 to Week 32	2/13	(15%)	12/51	(24%)	6/50	(12%)	0/9	(0%)	7/65	(11%)
Week 32 to Week 36	--	--	10/38	(26%)	9/32	(28%)	--	--	6/38	(16%)
Week 36 to Week 40	--	--	5/36	(14%)	4/30	(13%)	--	--	3/36	(8%)
Week 40 to Week 44	--	--	8/35	(23%)	6/30	(20%)	--	--	3/35	(9%)
Week 44 to Week 48	--	--	6/35	(17%)	3/29	(10%)	--	--	7/35	(20%)
Week 48 to Week 52	--	--	4/34	(12%)	4/28	(14%)	--	--	5/35	(14%)

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

Note: The numerator is the number of subjects requiring treatment for a gout flare in the time interval and treatment group being summarized. The denominator is the number of subjects exposed to at least 1 dose of that treatment in the time interval being summarized.
Study C02-009 was a 28-week trial that included placebo and febuxostat 240 mg QD treatment groups. Thus, there are no data after the Week 28 to 32 time interval for these 2 groups of subjects.

a Statistically significant difference versus allopurinol 300/100 mg QD ($p \leq 0.05$) using a CMH test stratified by study.

m Statistically significant difference versus febuxostat 120 mg QD ($p \leq 0.05$) using a CMH test stratified by study.

Cross-reference: Module 5.3.5.3.1, Statistical Table 3.2.2.27

Quality of life (QOL) data from the Phase 3 pivotal studies were not pooled. The SF-36, while a well-established general instrument, has not been studied in gout and the GAQ is a new instrument, which requires further validation. In addition, in subjects with gout, long-term treatment for greater than 1 year may be required for significant changes in QOL to be noted. However, a discussion of the results is presented below.
In Studies C02-009 and C02-010, the ability of febuxostat 80 mg QD and 120 mg QD to reduce and maintain serum urate level <6.0 mg/dL compared to the allopurinol 300 mg QD or 300/100 mg QD treatment group did not translate to significant improvements over allopurinol in QOL measures. Neither febuxostat nor allopurinol was able to consistently show QOL improvements over placebo. The induction of gout flares early in treatment with serum urate lowering therapy (which is known to occur) or the presence of tophi may explain the lack of QOL benefit at 6 or 12 months.

There are several other possible factors that should also be considered. The SF-36 questionnaire, while a well-established general instrument, may not be specific enough to actually capture gout-related differences between treatment groups. Also, the GAQ is a new instrument, and while initial analysis based on Phase 2 data provides support for the validity of the instrument, there are some areas in the questionnaire that require additional psychometric research before it can be concluded that the GAQ is a valid measure of gout-related outcomes.

Additional analyses of subpopulations using pooled data from the 2 pivotal trials are provided below. In each instance (age, gender, race, baseline serum creatinine, baseline serum urate levels, renal calculi etc), febuxostat shows evidence of efficacy compared either to placebo or to allopurinol.

Table 15 : Proportion of Subjects Whose Last 3 Serum Urate Levels Were <6.0 mg/dL by Age - ITT Subjects (Phase 3 Pivotal Studies)

	Placebo		Febuxostat 80 mg QD[a,#,m]		Febuxostat 120 mg QD[a,#]		Febuxostat 240 mg QD		Allopurinol 300/100 mg QD[#]	
Age	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
<45 years	0/36	(0%)	48/157	(31%)	80/150	(53%)	20/33	(61%)	12/166	(7%)
45-<65 years	0/79	(0%)	157/281	(56%)	184/286	(64%)	49/71	(69%)	63/270	(23%)
≥65 years	0/19	(0%)	57/79	(72%)	65/83	(78%)	23/30	(77%)	38/83	(46%)

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

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

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

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

Cross-reference: Module 5.3.5.3.1, Statistical Table 3.3

Table 16: Proportion of Subjects Whose Last 3 Serum Urate Levels Were <6.0 mg/dL by Gender - ITT Subjects (Phase 3 Pivotal Studies)

	Placebo		Febuxostat 80 mg QD[a,#,m]		Febuxostat 120 mg QD[a]		Febuxostat 240 mg QD		Allopurinol 300/100 mg QD[#]	
Gender	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
Male	0/123	(0%)	242/488	(50%)	313/498	(63%)	87/126	(69%)	101/491	(21%)
Female	0/11	(0%)	20/29	(69%)	16/21	(76%)	5/8	(63%)	12/28	(43%)

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

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

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

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

Cross-reference: Module 5.3.5.3.1, Statistical Table 3.3