



AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Febuxostat (FBX)

Proprietary Product Name: Adenuric

Sponsor: A Menarini Australia Pty Ltd

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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
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List of abbreviations

| Abbreviation | Meaning |
|--------------|---|
| ACR | American College of Rheumatology |
| AE | Adverse Event |
| ANOVA | Analysis of Variance |
| APTC | Antiplatelet Trialists' Collaboration |
| ARA | American Rheumatology Association |
| AUC | Area Under Curve |
| BMI | Body Mass Index |
| BSA | Body Surface Area |
| CI | Confidence interval |
| CL | Clearance |
| Cmax | Peak (or maximum) concentration |
| CrCl | Creatinine clearance |
| CRP | C-Reactive Protein |
| CS | Corticosteroids |
| CV | Coefficient of Variation |
| ECG | Electrocardiogram |
| FBX | Febuxostat |
| GAQ | Gout Assessment Questionnaire |
| GCP | Good Clinical Practice |
| Gral | Granulation Batch Size |
| IC50 | Febuxostat Concentration resulting in 50% decrease in serum urate |
| INR | International Normalised Ratio |
| ITT | Intention-to-Treat |
| LLQ | Lower Limit of Quantification |

| Abbreviation | Meaning |
|--------------|---|
| LOCF | Last Observation Carried Forward |
| NSAID | Non-Steroidal Anti-Inflammatory Drug |
| OLE | Open-Label Extension |
| PD | Pharmacodynamic |
| PK | Pharmacokinetic |
| PPS | Per Protocol Set |
| PY | Patient-Years |
| QOL | Quality-of-Life |
| SAE | Serious adverse event |
| SD | Standard Deviation |
| SEM | Standard Error of the Mean |
| SOC | System Organ Class |
| TSH | Thyroid Stimulating Hormone |
| T1/2 | Half-life of drug elimination |
| UGT | Uridine diphosphate Glucuronosyltransferase |
| ULN | Upper Limit of Normal |
| ULT | Urate Lowering Therapy |
| URTI | Upper Respiratory Tract Infection |
| VAS | Visual Analogue Scale |
| Vd | Volume of distribution |
| XO | Xanthine Oxidase |

1. Clinical rationale

Hyperuricaemia is defined as a serum or plasma urate concentration greater than 7.0 mg/dL (0.42 mmol/L). This value exceeds the limit of solubility of urate in extracellular fluid (6.8 mg/dL). Hyperuricaemia is usually the result of both increased uric acid production (from either endogenous or exogenous sources) and decreased uric acid excretion due to deficits in renal urate handling. The prevalence of hyperuricaemia in Caucasian males is estimated to be 5-

8%, but it is much higher in people of Polynesian and Chinese ethnicity. There is epidemiological data to suggest that the incidence and prevalence of symptomatic hyperuricaemia may be rising in developed countries (including Australia) due to several factors such as the increasing incidence of obesity and renal insufficiency, as well as changes in eating habits.

Symptomatic hyperuricaemia is a metabolic disorder in which tissue deposition of monosodium urate crystals from supersaturated body fluids results in attacks of inflammatory arthritis (acute gouty arthritis) and the development of macroscopic crystalline aggregates (tophi), primarily in the connective tissue. The plasma urate concentration is the single most important determinant of the risk of developing gout as there is a strong correlation between the incidence of acute gouty arthritis and mean serum urate concentration. Gout is rare in children and pre-menopausal females. Males are more commonly affected, and the peak age of onset in men is between 40 and 50 years of age. Gouty arthritis may be acute, acute-on-chronic or chronic. It usually begins in 1 joint (classically, the first metatarsophalangeal joint) but may affect multiple joints. Chronic tophaceous gout is a destructive and incapacitating condition affecting up to 20% of patients with gout. Symptomatic hyperuricaemia may also affect renal function by deposition of urate crystals in the renal interstitial tissue (urate nephropathy) and excretory tracts (nephrolithiasis).

Current approved treatment options in Australia for the management of hyperuricaemia include the XO inhibitor allopurinol and uricosuric drugs (for example probenecid and sulfipyrazone). However, significant proportions of patients either fail to respond to, or are intolerant of these treatment options. In addition, the current approved drugs have dosing limitations in patients with impaired renal function, which limit their optimal utilisation. As such there is an unmet need for additional therapies for management of symptomatic hyperuricaemia.

1.1. Guidance

A requirement for applications of new chemical entities of immediate release dosage forms is the provision of an absolute bioavailability study and a study to establish that the proposed formulation is optimal (for example, a study of the proposed commercial versus an oral solution of the drug). In the submission, the sponsor has provided acceptable justification for this variation of application requirement.

There are 2 specific regulatory guidelines pertaining to the requested indication. The TGA has adopted the EU guidelines "The Extent of Population Exposure to Assess Clinical Safety for Medicines Intended for Long-Term Treatment of Non-Life-Threatening Conditions" (effective 12 February 2002) and "Clinical Investigation of Medicinal Products for Long-Term use" (effective 12 February 2002).

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The submission contained the following clinical information:

- 32 clinical pharmacology studies, all of which provided Pharmacokinetic (PK) data, and 11 studies that provided Pharmacodynamic (PD) data.
- 2 population PK-PD analyses using data collected in Studies TMX-##-005 and C##-009.
- 2 pivotal efficacy/safety trials - Studies C##-009 and C##-010.
- 1 dose-finding study (TMX-##-004)

- 3 other efficacy/safety studies – one of which was a Phase III trial (Study F-GT##-153), and the other 2 trials were long-term open-label extension studies (TMX-##-005 and C##-021).
- Integrated Summary of Efficacy and Integrated Summary of Safety.
- The sponsor's Clinical Overview, Summary of Clinical Pharmacology Studies, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

2.2. Paediatric data

The submission did not include paediatric data.

2.3. Good clinical practice

All of the studies in the FBX clinical development program were conducted in accordance with the principles of Good Clinical Practice (GCP) and compliance with ethical requirements was met.

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each PK topic, and the location of each study summary.

Table 1. Submitted Pharmacokinetic Studies

| PK topic | Subtopic | Study ID |
|---------------------------|---------------------------------------|--|
| PK in healthy adults | General PK - Single dose | TMX-##-01 and C##-040 |
| | - Multi-dose | TMX-##-001 and C##-023 (USA), as well as |
| | | TMX-##-03 and TMX-##-05 (Japan) |
| | Bioequivalence† - Multi-dose only | TMX-##-009, TMX-##-010, TMX-##-018, C##-033, C##-034 and C##-044 |
| | Food effect | TMX-##-002 C##-036 C##-054 |
| PK in special populations | Target population § - Multi-dose only | TMX-##-009 and TMX-##-010 (Japan); as well as TMX-##-004 (USA) |
| | Hepatic impairment | TMX-##-012 (US) |
| | Renal impairment | TMX-##-008 (US) and TMX-##-08 (Japan) |

| PK topic | Subtopic | Study ID |
|------------------------|----------------------|------------------------------------|
| | Elderly | TMX-##-016 (US) |
| Gender-related PK | Males versus Females | TMX-##-016 (US) |
| PK interactions | Colchicine | TMX-##-006 and C##-006 |
| | Indomethacin | TMX-##-017 |
| | Naproxen | C##-013 |
| | Hydrochlorthiazide | C##-059 |
| | Desipramine | C##-005 |
| | Antacid medication | TMX-##-014 |
| | Rosiglitazone | TMX-##-103 |
| | Theophylline | TMX-##-101 |
| | Warfarin | C##-057 and F-P1##-162 |
| Population PK analyses | Healthy subjects | Nil |
| | Target population | TMX-##-005 and C##-009 (Sub-study) |

† Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the PK studies had deficiencies that excluded their results from consideration.

4. Summary of pharmacokinetics

The information in the following summary is derived from conventional PK studies unless otherwise stated.

4.1. Physicochemical characteristics of the active substance

The active substance is a new chemical entity designated as a 2-arylthiazole derivative designated as 2-[3-cyano-4-(2-methylpropoxy) phenyl]-4-methylthiazole-5-carboxylic acid. It is non-purine, selective inhibitor of XO, which prevents the normal oxidation of purines to uric acid. The molecular weight of FBX is 316.37. This information has been obtained from summaries in the submission. In Vitro tests demonstrate the B1 tablet formulation optimally dissolves at the physiologically relevant pH range of 6.0-7.5.

4.2. Pharmacokinetics in healthy subjects

4.2.1. Absorption

4.2.1.1. *Sites and mechanisms of absorption*

Following oral dose administration FBX is rapidly and extensively absorbed from the gastrointestinal tract with a T_{max} of 1.0-1.8 hours, and > 84% absorbed (postulated from data in Study C##-040 in which only 6-16% of radioactivity was recovered as unchanged FBX in the faeces). There is no accumulation of FBX following multiple occasions of once daily dosing. After single or multiple oral 40 mg and 80 mg once daily doses, C_{max} is approximately 1.5 to 1.6 $\mu\text{g}/\text{mL}$ and 2.5 to 2.6 $\mu\text{g}/\text{mL}$, respectively.

4.2.2. Bioavailability

4.2.2.1. *Absolute bioavailability*

Absolute bioavailability has not been determined in humans because of the unavailability of an intravenous formulation of FBX.

4.2.2.2. *Bioavailability relative to an oral solution or micronised suspension*

The clinical section of the submission did not contain information about drug bioavailability relative to an oral solution, which is a TGA recommendation for new immediate-release oral dose forms such as FBX. The purpose of the request is to demonstrate that the dose form has been optimally formulated.

4.2.2.3. *Bioequivalence of clinical trial and market formulations*

The proposed commercial formulation and dosage strengths of FBX to be made available in Australia are similar to the 80 mg and 120 mg tablet strengths of the B1 formulation.

4.2.2.4. *Bioequivalence of different dosage forms and strengths*

The bioequivalence of different FBX formulations has been determined in 6 separate Phase I bioavailability studies (TMX-##-009 [n = 25], TMX-##-010 [n = 27], TMX-##-018 [n = 26], C##-033 [n = 33], C##-034 [n = 34] and C##-044 [n = 35]). The formulations evaluated were the Company C 20 mg tablet, Formulation A 20 and 80 mg tablets, Formulation B 20 and 80 mg tablets, and Formulation B1 20, 40, 80 and 120 mg tablets. Bioequivalence was achieved when the 90% Confidence Intervals (CIs) for the ratio of 1 formulation to another for C_{max} , AUC_t and AUC_∞ were within the acceptable range of 0.80-1.25. For all the bioavailability studies, FBX (single dose) was taken in the morning following a 10-hour overnight fast. Subjects were otherwise healthy and aged between 18 and 55 years (mean age 31 years). Just over half of all recruited subjects were male (56.1%; 101/180). All of the bioequivalence studies were randomised, open-label, single centre trials with a crossover design of 2-4 study periods. More than 93% of recruited subjects in each of the 6 studies received FBX in all designated study periods.

The following formulations were compared in each of the studies:

- Study TMX-##-009: Formulation A 20 mg versus Company C 20 mg; and Formulation A 80 mg versus Formulation A 20 mg x 4 tablets,
- Study TMX-##-010: Formulation A 20 mg versus Formulation B 20 mg; and Formulation B 80 mg versus Formulation B 20 mg x 4 tablets,
- Study TMX-##-018: B1 Formulation 20 mg versus Company C 20 mg; and Formulation B1 80 mg versus Formulation B1 20 mg x 4 tablets (B1 formulation was manufactured at 75 L granulation [Gral] batch size, that is small scale production facility),

- Study C##-033: B1 Formulation 80 mg versus B1 Formulation 40 mg x 2 tablets (both manufactured at 300 L Gral batch size, that is the proposed commercial batch size production),
- Study C##-034: B1 Formulation 80 mg (300 L Gral) versus B1 Formulation 80 mg (75 L Gral), and
- Study C##-044: B1 Formulation 120 mg versus B1 Formulation 80 mg plus B1 Formulation 40 mg (all manufactured at 300 L Gral).

The Phase I and II clinical studies used the Company C 20 mg tablet formulation, and the pivotal Phase III trials used the B1 formulation, which is very similar to the proposed commercial formulation. The 20 mg tablet formulations of B1 and Company C demonstrated bioequivalence in Study TMX-##-018. In addition, bioequivalence was demonstrated for the combinations of tablet strengths (20, 40, 80 and 120 mg) used in the clinical studies (as demonstrated in Studies TMX-##-018, C##-033 and C##-044), as well as for tablets manufactured at the pilot production scale of 75 L Gral versus the 300 L Gral commercial production size (Study C##-034). For the formulations used in the clinical trials (Company C and Abbott B1 Formulation), the mean T_{max} values for FBX were 1.5-2 hours across the bioequivalence studies. Mean FBX C_{max} were 3.0-3.5 $\mu\text{g}/\text{mL}$ after an 80 mg dose, and 5.0 $\mu\text{g}/\text{mL}$ following a 120 mg dose. Mean FBX AUC_{∞} values were approximately 10 $\mu\text{g.h}/\text{mL}$ after an 80 mg dose, and 17 $\mu\text{g.h}/\text{mL}$ following a 120 mg dose.

4.2.2.5. *Influence of food*

The effect of food on the PK of FBX has been investigated in 3 studies involving otherwise healthy subjects: 2 Phase I single-dose studies following oral dosing with FBX 40 mg (Study TMX-##-002) or 120 mg (Study C##-054); and 1 Phase I multiple-dose study evaluating FBX 80 mg once daily for 6 consecutive days. Study C##-036 was a single-centre (USA), randomised, open-label trial with a 2-period crossover period conducted between December 2002 and January 2003.

The 3 food studies yielded similar results, namely a decrease in FBX C_{max} by 38-49%, and a decrease in AUC_{∞} by 16-19%, following a high fat meal compared to drug ingestion under fasted conditions. In addition, T_{max} was delayed by as much as 1 hour. However, the sponsor recommends that FBX can be taken with or without food (as per the proposed PI) because there is no substantial difference in the reduction in serum urate level under fasting (58% reduction) versus non-fasting conditions (51% reduction). In the Phase III studies, the patients were given no specific instruction on whether or not their study medication (including FBX) was taken under fasted or non-fasting conditions.

4.2.2.6. *Dose proportionality*

A total of 5 single centre studies have been conducted in healthy subjects to determine dose proportionality – 2 trials in the USA (Studies TMX-##-001 and C##-023) and 3 in Japan (Studies TMX-##-01, TMX-##-03 and TMX-##-05). All of the studies were of multiple dose design apart from Study TMX-##-01(single dose only). FBX was given in daily doses ranging from 10 to 300 mg.

Study TMX-##-001 was a randomised, placebo-controlled, dose-escalation study, which enrolled 154 healthy subjects (87 male) between the ages of 18 and 55 years. It consisted of 12 FBX dose groups, each containing 12 subjects (10 receiving FBX and 2 given placebo). However, 1 dose group (FBX 50 mg/day) was repeated because in the first dose panel 3 subjects had possible traces of xanthine crystals detected in their urine. The PK (and PD) of FBX was determined in 118 subjects following single (day 1) and multiple daily doses (days 3-14) of FBX, ranging from 10-240 mg. The FBX doses examined included once daily 10, 20, 30, 40, 50, 70, 90, 120, 160, 180 and 240 mg (given in the morning); as well as FBX 30 mg twice daily. The study was conducted between November 1999 and April 2001. FBX 10-240 mg was rapidly absorbed

with a mean T_{max} ranging from 0.7-1.44 hours on days 1-14. The PK parameters of FBX were not time or dose dependent, and remained linear in the dose range of 10-120 mg once daily. When the dose of FBX exceeded 120 mg/day, a greater than dose proportional increase in AUC was observed, which is postulated to be due to an increase in the extent of enterohepatic recycling of FBX (that is increased biliary excretion of the glucuronide conjugate of FBX). At steady state, only a small percentage (0.9-6.1%) of FBX was excreted in the urine as parent drug, indicating that the renal excretion of FBX is not a major route of drug elimination. A greater proportion of the FBX dose was excreted in the urine as the conjugated metabolite of FBX (versus oxidated metabolite) indicating that conjugation is the major metabolic pathway in the metabolism of FBX.

Part A of Study C##-023 examined the PK (and PD) of FBX 300 mg once daily for 7 days in 10 healthy subjects (12 enrolled-2 received placebo). The USA based study recruited 6 male and 6 female subjects between the ages of 25 and 65 years. Following administration of FBX 300 mg/day for 7 days, the mean T_{max} value was 1.0 hour, and the mean dose-normalized C_{max} was statistically equivalent ($p > 0.05$) to C_{max} values observed in the dose-escalation study TMX-##-001 (FBX 10-240 mg/day). Again only a small fraction of the 300 mg dose (1.3%) was recovered in the urine as parent drug.

The 3 Japanese studies (TMX-##-01, TMX-##-03 and TMX-##-05) recruited a total of 63 healthy male subjects (no female subjects). The 3 trials examined low doses of FBX (0.2-50 mg/day), taken as either single doses (TMX-##-01) or multiple FBX doses over 7 days (TMX-##-03 and TMX-##-05). The 3 studies showed results consistent with each other and the USA based trials, with T_{max} ranging from 0.8-1.5 hours, and dose dependent increases in mean C_{max} and AUC values.

4.2.2.7. *Bioavailability during multiple-dosing*

No drug accumulation was observed with multiple once daily dosing of FBX (and twice daily dosing, up to 30 mg twice daily) in the 4 dose proportionality studies described above that had multiple FBX doses administered over 7-14 day time periods.

4.2.2.8. *Effect of administration timing*

In all but 2 of the human studies, FBX was administered once daily, in the morning. However, in Study TMX-##-001, 11 healthy subjects received FBX 30 mg twice daily for 11 days. The evening dose of FBX resulted in a slight decrease in C_{max} and a minor delay in T_{max} when compared to the morning dose administration of FBX. However, the total exposure (AUC) to FBX and its metabolites was similar in subjects with diurnal versus once daily morning administration of FBX.

In the Phase I Study TMX-##-003, FBX 10 mg was given twice daily to 16 subjects (patients were supposed to have hyperuricaemia at baseline, defined as a serum uric acid level between 8.0 and 12.0 mg/dL on day -1, but none did so) and compared with 3 other regimens (FBX 20 mg once daily, FBX 40 mg once daily, and placebo twice daily). Each of 4 treatment arms had a blinded dose of study medication before breakfast (0800 hours), and a dose after dinner (2000 hours). A total of 64 subjects (35 male) aged between 30 and 85 years enrolled in this randomised study, and 61 completed the 14-day investigation period. This study demonstrated a similar result to TMX-##-001 in that there was a delay in T_{max} , and a decrease in C_{max} for the evening versus morning dose, for the subjects who took FBX 10 mg twice daily. However, overall FBX exposure (as determined by AUC over 12 hours post-dosing) was only slightly decreased for the evening versus morning dose administration of FBX.

4.2.3. *Distribution*

4.2.3.1. *Volume of distribution*

By combining data from 15 Phase I studies, FBX appears to have a low to medium volume of distribution (Vd) of approximately 0.7 L/kg. Collectively, in the Phase I trials, 247 subjects

received single doses of FBX (n = 183 for 80 mg, and n = 64 for 120 mg), and 130 healthy subjects were administered multiple doses of FBX (n = 121 for 80 mg/day and n = 9 for 120 mg/day). The apparent steady-state Vd of FBX ranges from 29 to 75 L after oral doses of 10 mg to 300 mg (Studies TMX-##-001 and C##-023). The population PK analyses estimate the mean apparent Vd for FBX to be 54.4 L. No consistent change in Vd between age groups (Study TMX-##-016), and varying degrees of hepatic impairment (Study TMX-##-012) has been observed. However, in Study TMX-##-008, there was a 23-49% increase in Vd in subjects with moderate or severe renal impairment.

4.2.3.2. *Plasma protein binding*

As demonstrated in 2 in vitro studies, FBX is highly bound to human plasma proteins (97.9-99%), predominately to albumin (98.1-99.1%), mainly at the diazepam-binding sites (Study C##-023, and a pre-clinical study). Plasma-protein binding is constant over the concentration range achieved with FBX 40 mg and 80 mg doses. There were no differences in the extent of protein binding between young people (18-40 years of age) compared to elderly (> 65 years of age) subjects, between male and female subjects, or in subjects with varying degrees of hepatic impairment (mild-moderate). In subjects with renal impairment, a slight decrease in protein binding of FBX with increasing renal impairment has been observed (98.8% in subjects with severe renal impairment versus 99.1% in subjects with normal renal function). Binding of metabolites 67-M1, 67-M2 and 67-M4 to plasma proteins was less than observed with the parent compound at approximately 90%, 81.7% and 91.7%, respectively.

4.2.4. *Metabolism*

4.2.4.1. *Sites of metabolism and mechanisms / enzyme systems involved*

FBX is eliminated from the blood mainly by metabolism to glucuronide conjugates in the liver, and to a much lesser degree by oxidative metabolism via cytochrome P450 (CYP450), also in the liver. The glucuronide conjugate of FBX formed by several uridine diphosphate glucuronosyltransferase (UGT) isoforms including UGT1A1, UGT1A8, and UGT1A9 is not active, and therefore does not contribute to the efficacy of FBX. Oxidation of FBX, formed primarily by the CYP450 isoforms 1A1, 1A2, 2C8, and 2C9, leads to 3 pharmacologically active metabolites, 67-M1, 67-M2 and 67-M4. These oxidative metabolites also undergo glucuronide conjugation to form inactive metabolites. The metabolites of FBX that are detectable in human plasma are found at much lower concentrations compared to parent drug. While the glucuronide conjugates are eliminated in the urine, less than 4% of orally administered FBX is eliminated in the urine as unchanged drug.

4.2.5. *Excretion*

4.2.5.1. *Routes and mechanisms of excretion*

Following administration of radiolabelled FBX, the parent drug accounted for 84% - 94% of total plasma radioactivity through to 4 hours following dosing (Study C##-040). This open-label, Phase I study evaluated 6 young, healthy male Caucasian subjects for the metabolism and excretion of radiolabelled [¹⁴C] FBX for up to 7 days after receiving a single 80 mg dose. Only 8-16% of the administered [¹⁴C] FBX dose was recovered unchanged in the faeces, with known FBX metabolites accounting for the vast majority of the remaining dose recovered in the faeces. FBX undergoes extensive glucuronidation, with the majority of the glucuronide metabolite being eliminated into the intestine via the bile, and cleaved by intestinal β -glucuronidase. Pre-clinical animal studies show that the intestinal released FBX metabolite can then be either recycled in the enterohepatic system, or excreted in the faeces.

The half-life (T_{1/2}) of FBX in the plasma ranges from 5 to 8 hours, and reaches steady state within 1 week of once daily dosing.

4.2.6. Renal clearance

The renal clearance of FBX is highly variable, but typically less than 0.35 L/h. In studies TMX-##-001 and Part A of C##-023, the mean estimates of renal clearance of FBX for healthy subjects over the 10-300 mg dose range were variable, and ranged from 0.05-0.35 L/h. Age, gender and hepatic impairment did not have an effect on renal FBX clearance in Studies TMX-##-016 and TMX-##-012. However, renal clearance was significantly lower in otherwise healthy subjects with renal impairment (0.12-0.13 L/h for mild and moderate renal impairment; and 0.06 L/h for severe renal impairment) versus those with normal renal function (renal Cl 0.24 L/h) in Study TMX-##-008.

The urinary excretion of unchanged FBX is also highly variable, but accounts for less than 4% of the administered dose. The urinary excretion of unchanged FBX is unaffected by increasing dose, repeated ingestion, age and gender (Studies TMX-##-001 and TMX-##-016). However, subjects with mild or moderate hepatic impairment tend to have slightly higher urinary excretion of unchanged FBX (3.2-3.3% of total oral dose) compared to those with normal liver function (2.4%; Study TMX-##-012). For subjects with severe renal impairment (CrCl 10-29 mL/min), the fractional excretion of unchanged FBX is lower (0.8%) compared to healthy control subjects with normal renal function (1.7%) and mild-moderate renal impairment (1.3-1.7%; Study TMX-##-008).

4.2.7. Intra- and inter-individual variability of pharmacokinetics

An assessment of the intra-subject and inter-subject variability for the PK of FBX was obtained from 6 Phase I bioequivalence studies (TMX-##-009 [n = 25], TMX-##-010 [n = 27], TMX-##-018 [n = 26], C##-033 [n = 33], C##-034 [n = 34] and C##-044 [n = 35]). The results indicate that the intra-subject variability of FBX is low for C_{max} (CVs of 23-34%) and AUC_{∞} (CVs of 9-12%). The inter-subject variability appears to be slightly higher but overall remains low (CVs of 27-48% for C_{max} and CVs of 23-39% for AUC_{∞}). The different formulations tested (Teijin and Abbott A, B and B1) and/or tablet strengths (20, 40, 80 and 120 mg) did not appear to affect the intra- or inter-subject variability of FBX. For T_{max} , the intra- or inter-subject variability was moderately high (CVs of 41-73% and 54-90%, respectively) but there were no relevant differences between the investigated FBX formulations or tablet strengths for T_{max} .

4.2.8. Pharmacokinetics in the target population

The PK data in the target population is provided by:

- 2 Phase II Japanese studies (TMX-##-009 and TMX-##-010), which evaluated 138 subjects with hyperuricaemia (baseline serum urate level > 8.0 mg/dL),
- 1 USA centred, Phase II trial (Study TMX-##-004) which enrolled 154 subjects with hyperuricaemia and gout, and
- 2 population PK-PD analyses - Study TMX-##-005 (extension phase of Study TMX-##-004), and a sub-study of the pivotal Phase III trial C##-009.

In both of the Japanese studies, subjects received FBX once daily after breakfast for 6-8 weeks at doses of 10, 20 and 40 mg. The 2 trials recruited a total of 138 subjects (135 male) aged between 20 and 65 years. In almost all of the subjects, the T_{max} of the metabolites was almost identical to the T_{max} of the parent (unchanged) drug. Furthermore, the results suggested that the $T_{1/2}$ of 8.17 +/- 2.41 hours was slightly prolonged in hyperuricaemic patients compared to healthy male subjects (that is versus data recorded in Phase I Japanese studies). However, when considering the dose ratio, AUC and C_{max} for unchanged FBX in hyperuricaemic patients is similar to that observed in healthy male control subjects.

In Study TMX-##-004, trough plasma (unchanged and total) and urine (free and total) concentrations of FBX were collected on days 1, 7, 14, 21 and 28. Blood samples were also collected on days -14 and -2 (that is prior to commencement of FBX). A total of 153 (136 male)

subjects with hyperuricaemia and gout were recruited into this study, and randomly allocated to 1 of 4 treatment arms (placebo; and FBX 40, 80 and 120 mg/day). Most (145 patients) completed the 28-day study period and provided at least 1 sample for PK analysis. However, PK results were limited as many subjects (particularly those who received FBX 40 mg) had pre-dose plasma and urine free FBX concentrations below the lower limit of quantification for the assay. Following multiple dosing with FBX, the mean trough concentrations of FBX were 5-17 fold higher than those of the free urinary FBX concentration.

Two population PK analyses were performed using data from Study TMX-##-005, and Study C##-009. The structural model was a 2-compartment model with first order absorption rate and a lag time. The PK model estimated population means for Cl , V_c (Vd of the central compartment), V_p (Vd of the peripheral compartment), Q (distribution clearance), K_a (absorption rate constant), and T_{lag} (absorption lag time). The population PK analysis included 125 subjects (out of a possible 665) receiving FBX (80, 120 and 240 mg once daily) in the Phase III Study C##-009, and 87 (of a possible 116) subjects in the open label, extension Study TMX-##-005. In both studies, PK (and PD) samples were taken at steady state (6 PK samples collected between weeks 16-28 in Study C##-009, and 3 samples acquired between weeks 28-52 in Study TMX-##-005). In general, the PK parameters derived in the population PK analyses (that is patients with hyperuricaemia and gout) were consistent with that observed in the Phase I studies (that is healthy subjects). The population PK data from Study TMX-##-005 identified baseline CrCl and smoking status as statistically significant covariates for determining drug clearance. Based on the findings of this population PK analysis, a subject with CrCl of 20 mL/min had a 30% lower clearance of FBX, and a 44% higher plasma exposure to FBX in comparison to a subject with a CrCl of 120 mL/min. This result is consistent with that observed in the Phase I renal impairment study (TMX-##-008).

The population PK data from Study C##-009 identified baseline CrCl, body weight and co-administration of fibrate therapy as statistically significant covariates for determining clearance. However, smoking could not be confirmed as a significant covariate affecting clearance in Study C##-009. Concomitant fibrate therapy decreased FBX clearance by approximately 17%, and increased FBX exposure by 21%.

4.2.9. Pharmacokinetics in other special populations

4.2.9.1. *Pharmacokinetics in subjects with impaired hepatic function*

Study TMX-##-012 was a Phase I, open-label, parallel-group trial with the primary objectives of comparing the PK/PD and safety of FBX 80 mg once daily for 7 consecutive days in otherwise healthy subjects with varying degrees of hepatic impairment to subjects with normal hepatic function. A total of 28 subjects between the ages of 30 and 70 years of age (15 male and 13 female) were enrolled into 3 different hepatic function groups (balanced for gender, weight and age) based on the Child-Pugh classification of hepatic function at screening: normal hepatic function ($n = 11$), mildly impaired (Child-Pugh A; $n = 8$), or moderately impaired (Child-Pugh B; $n = 8$). The study was conducted at 2 investigator sites in the USA between September 2001 and May 2002. Subjects were admitted to a study confinement facility for 2 periods. The first confinement began at 1600 hours on day -2 until all study procedures were completed on day 2. The second confinement began at 1730 hours on day 6 and continued until day 8. The main PK parameters (FBX and the 3 active metabolites) assessed were C_{max} , T_{max} , AUC_t (from zero until the last quantifiable concentration), AUC_{24} (for the dosing interval), and the total amount and fraction of the dose excreted in the urine over 24 hours. All the PK parameters were tabulated and analysed using descriptive statistics (for example mean, SD and coefficient of variation [CV %]). The relationship between hepatic function and the PK plasma and urine parameter of interest were analysed via ANOVA, using hepatic function as the factor.

The mean FBX T_{max} values for subjects with normal hepatic function (1.23 hours) were similar to those in subjects with mild (1.25 hours) and moderate (0.75 hours) hepatic impairment. The

extent of total plasma exposure to FBX was higher in subjects with mild or moderate hepatic impairment (mean FBX unbound C_{max} values 24% higher; and mean unbound AUC_{24} values 24-28% greater), but the differences compared to subjects with normal hepatic function were not statistically significant. No significant PK effect (mean C_{max} and AUC values) was observed in the active metabolites of FBX (67M-1, 67M-2 and 67-M4) related to hepatic function (normal or impaired). However, with increasing hepatic impairment there was an increase in the amount of the fraction excreted in the urine as total FBX (by up to 29% in subjects with moderate hepatic impairment) suggesting that hepatic impairment causes a decrease in the biliary excretion of FBX. The sponsor proposes that the data in this trial supports the recommendation that no dose adjustment with FBX is required for patients with mild or moderate hepatic impairment. This is an acceptable opinion but a significant limitation to this study is that the Child-Pugh has not been developed or validated for predicting drug elimination. The Child-Pugh classification system was developed for categorising the severity of hepatic impairment.

4.2.9.2. *Pharmacokinetics in subjects with impaired renal function*

Study TMX-##-008 was a Phase I, open-label, parallel-group trial with the primary objectives of evaluating the PK/PD and safety of FBX 80 mg once daily for 7 consecutive days in otherwise healthy subjects with varying degrees of renal impairment and subjects with normal renal function. The higher FBX dose of 120 mg/day was not investigated. A total of 31 subjects between the ages of 30 and 70 years of age (18 male and 13 female) were enrolled into 4 different renal function groups based on their creatinine clearance (CrCl) results (Cockcroft-Gault method) at screening: normal renal function ($CrCl > 80mL/min$; $n = 11$), mild renal impairment ($CrCl 50-80 mL/min$; $n = 6$), moderate renal impairment ($CrCl 30-49 mL/min$; $n = 7$) and severe renal impairment ($CrCl 10-29 mL/min$; $n = 7$). The study was conducted at 3 investigator sites in the USA between May and December 2001. The method of study confinement, PK parameters of interest and statistical analysis was the same as Study TMX-##-012.

The mean FBX T_{max} (0.93-1.33 hours) and unbound C_{max} values (0.0243-0.0359 $\mu\text{g}/\text{mL}$) for subjects with varying degrees of renal insufficiency were similar to those in subjects with normal renal function. However, with increasing renal impairment unbound FBX AUC_{24} values consistently rose (from 0.0655 $\mu\text{g}.\text{h}/\text{mL}$ in those with normal renal function to 0.149 $\mu\text{g}.\text{h}/\text{mL}$ in subjects with moderate renal impairment). A statistically significant linear relationship between unbound FBX AUC_{24} and CrCl was identified. Fitted FBX unbound AUC_{24} values from the regression model for a subject at approximately the midpoint CrCl for each renal impairment group differed from that of the normal renal function arm by as much as 76%. FBX half-life also tended to increase with worsening renal function (4.7 hours in those with normal renal function versus 7.0 hours in subjects with moderate renal impairment). The active metabolites (67M-1, 67M-2 and 67-M4) also showed the same statistically significant relationship between mean AUC_{24} values and worsening CrCl. As expected, the urinary excretion of unchanged and total FBX from plasma was sequentially lower in each group of subjects with worsening renal impairment. In summary, the exposure to FBX and its 3 active metabolites appears to increase with worsening renal impairment. However, the sponsor states that the maximum C_{max} and AUC values observed in Study TMX-##-008 in subjects with mild-moderate renal impairment does not exceed the drug exposure levels seen in healthy subjects who safely received FBX 240 mg/day for up to 14 days in other trials (in particular, Study TMX-##-001).

Study TMX-##-08 was a Phase II, open-label, parallel-group trial conducted in 7 sites in Japan in 2001, which evaluated the PK/PD and safety of a single 20 mg dose of FBX (taken in the morning, 30 minutes after breakfast) in otherwise healthy subjects with mild ($CrCl 30-49 mL/min$; $n = 5$) to moderate ($CrCl 50-80 mL/min$; $n = 5$) renal impairment and subjects with normal renal function ($CrCl > 80/\text{min}$; $n = 5$). Of the 15 recruited subjects, 13 were male. The mean FBX T_{max} was delayed (from 0.9 to 1.3 hours) and the mean C_{max} decreased (by up to 24%) in subjects with mild or moderate renal insufficiency. However, mean FBX AUC values

decreased in subjects with mild renal impairment, but increased in those with moderate renal insufficiency. In terms of the active metabolites, mean C_{max} values were similar across the 3 groups, but mean AUC tended to increase with worsening renal function. As expected, the urinary excretion of unchanged and total FBX from plasma was sequentially lower in each group of subjects with worsening renal impairment compared to subjects with normal renal function.

4.2.9.3. *Pharmacokinetics according to age and gender*

Study TMX-##-016 was a Phase I, open-label, parallel-group trial with the primary objective of evaluating the effect of age and gender on the PK/PD and safety of FBX 80 mg once daily for 7 consecutive days (taken after an overnight fast of at least 8 hours). A total of 48 healthy subjects were enrolled into the study: males aged 18-40 years ($n = 12$), males aged ≥ 65 years ($n = 12$), females aged 18-40 years ($n = 12$), and females aged ≥ 65 years ($n = 12$). The trial protocol did not set an upper age limit for inclusion. In the subjects ≥ 65 years of age, 12 (9 males and 3 females) were > 70 years. The oldest subject in the cohort was a 76-year-old male. The study was conducted at a single investigator site in the USA in December 2001. The method of study confinement, PK parameters of interest and statistical analysis was the same as Study TMX-##-012.

The mean FBX T_{max} and unbound C_{max} values for subjects ≥ 65 years were similar to those in subjects aged 18-40 years (0.99 hours versus 0.94 hours for T_{max} ; and 0.0272 versus 0.0279 $\mu\text{g}/\text{mL}$ for C_{max} ; $p > 0.05$). The mean unbound AUC_{24} for subjects ≥ 65 years was only approximately 10% higher than that for younger subjects and this comparison was not statistically significant ($p > 0.05$). No age related changes in the fractional urinary excretion of FBX was observed indicating there is no significant change in the conjugation of FBX with advancing age. The mean AUC_{24} values for the 3 active metabolites were 6-18% higher in the older subjects but none of these differences were statistically significant ($p > 0.05$).

In the same study, the PK characteristics of FBX were compared by gender (24 males and 24 female subjects). In female subjects, the mean FBX unbound C_{max} and AUC_{24} values were higher (33% and 16%, respectively) than those seen in male subjects, and this difference was statistically significant ($p < 0.05$). However, when body weight was used as a covariate in the ANCOVA evaluation, no statistically significant difference for mean FBX unbound C_{max} and AUC_{24} values was identified. This result suggests that the differences in body weight between genders accounted for much of the difference in these PK parameters. Fractional urinary excretion of FBX was similar between males and females, indicating there is no significant change in the conjugation of FBX with gender. The mean AUC_{24} values for the 3 active metabolites were also similar between the genders, with no statistically significant ($p > 0.05$) differences being observed.

4.2.9.4. *Pharmacokinetics related to genetic factors*

No specific studies have examined this area.

4.2.10. *Pharmacokinetic interactions*

4.2.10.1. *Pharmacokinetic interactions demonstrated in human studies*

A total of 10 *in vivo* drug-drug interaction studies in humans have been performed. The results indicate that colchicine (Study TMX-##-006), indomethacin (Study TMX-##-017), and hydrochlorothiazide (C##-059) do not have clinically significant effects on the PK of FBX, and therefore, no dose adjustment for FBX is necessary when it is co-administered with these drugs. Likewise, these studies demonstrate that FBX has no clinically significant effects on the PK of indomethacin, or colchicine, and therefore, no dose adjustment for these drugs is considered necessary when they are co-administered with FBX.

However, a potentially significant drug-drug interaction was observed in Study C##-013 with the combination of FBX (80 mg once daily for 7 days) and naproxen (500 mg twice daily for 7 days). Co-administration of naproxen increased the C_{max} , AUC_{0-24} , and half-life of FBX by

approximately 28%, 41%, and 26%, respectively, in comparison with FBX alone. Furthermore, the mean oral clearance of FBX decreased by 28% when it was given combination with naproxen compared to monotherapy. This observation was suggested to be due to inhibition of glucuronidation by naproxen. Nonetheless, the increase in FBX plasma exposure is not expected to raise any safety concerns, and no dose adjustment for FBX is recommended when the drug is co-administered with naproxen.

A drug-drug interaction study (Study C##-005) has demonstrated that FBX has slight inhibitory effect on desipramine, a CYP2D6 substrate. However, no dose adjustment is considered necessary for drugs that are CYP2D6 substrates when they are co-administered with FBX.

Study TMX-##-014 examined the effect of a liquid antacid containing magnesium hydroxide and aluminium hydroxide on the PK of FBX. This demonstrated that the co-administration of antacid delays the absorption of FBX (mean increase in T_{max} of 1 hour), decreases the C_{max} of FBX by a mean of 31%, but AUC is unchanged compared to when FBX is taken alone. However, the decrease in FBX AUC is unlikely to be of clinical relevance as there is a good correlation between total FBX AUC and change in serum urate level.

Study TMX-##-103 was a Phase I, double-blind, randomized, 2-period cross-over trial conducted at a single site in USA which examined the effect of multiple doses of FBX (120 mg daily for 9 consecutive days) on the PK of a single 4 mg oral dose of rosiglitazone (taken on day 5) and its metabolite, N-desmethylrosiglitazone. The study recruited 39 otherwise healthy patients (27 male and 12 female) between the ages of 22 and 52 years. In this submission, only the protocol of Study TMX-##-103 was provided. The sponsor will be asked to provide the final study report with results for this trial in this report.

A theophylline interaction study (TMX-##-101) has been performed, which evaluated the effect of multiple oral doses of FBX on the PK of a single dose of theophylline. Theophylline is a methylxanthine drug, which undergoes metabolism via CYP1A2 and XO. It is metabolized by the CYP450 system to form 1-methylxanthine, which is then converted to 1-methyluric acid. The latter process is mediated by XO. FBX is a non-purine selective inhibitor of XO, and as such may affect XO mediated metabolism of theophylline, resulting in potentially altered clearance of theophylline. Since theophylline is a narrow therapeutic index drug and co-administration with high doses of another XO inhibitor (allopurinol) results in decreased clearance of theophylline, Study TMX-##-101 was conducted to evaluate the effect of FBX at steady-state on the PK of theophylline (C_{max} and exposure as determined by AUC). Neither the mean clearance nor the mean half-life values of theophylline were affected by the co-administration of FBX. Therefore, co-administration of FBX with theophylline had no effect on the PK (or likely safety) of theophylline.

Two of the 10 drug-drug interaction studies (C##-057 and F-P1##-162) involving healthy subjects have demonstrated that multiple doses of FBX (B1 formulation) have no clinically significant effects on the PK or PD of concomitantly administered warfarin. Both studies were of similar design, with two 14-28 day crossover periods. There was no washout phase between the 2 crossover periods in order to limit the extent of each subject's exposure to warfarin, and to minimize the potential for INR instability. Study C##-057 recruited 22 healthy subjects (21 male), and examined the effect of multiple doses of FBX 120 mg/day on the PK and PD of warfarin (BMS formulation). Subjects having met the entry criteria received warfarin for a lead-in period of 9 days. All subjects received 5 mg/day of warfarin on days 1 and 2, and thereafter the dose was adjusted according the daily International Normalization Ratio (INR) reading. The target INR range was 1.2-1.8 between days 3-9, but only subjects in the INR range of 1.5-1.8 on days 7-9 for eligible for PK evaluation. The second study (F-P1##-162) increased the number of subjects (n = 32; and 28 achieved the target INR range for evaluation), increased the duration of the warfarin lead-in period (from 9 to 12 days), examined the effect of multiple doses of FBX 80 mg (versus 120 mg in Study C##-057), and required a stable INR of ≥ 1.5 to ≤ 2.0 for 3 days prior to subject randomization.

Both of these studies demonstrated that multiple oral doses of FBX 80 mg and 120 mg had no effect on the PK of R- or S-warfarin at steady-state – refer to Tables 6A and 6B.

4.2.11. Clinical implications of in vitro findings

Potential drug-drug interactions based on changes in protein binding are unlikely with FBX as in vitro protein-binding studies indicated that warfarin, digoxin, ibuprofen, captopril, bezafibrate, verapamil, and nitrendipine did not affect the protein binding of FBX in human plasma.

In addition an in vitro human hepatocyte enzyme-induction study showed that FBX was not associated with induction of CYP450 isoforms 1A1/2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4/5, and therefore, it is considered that there is low potential for *in vivo* drug-drug interactions with FBX due to induction of liver CYP450.

4.3. Evaluator's overall conclusions on pharmacokinetics

In this submission, the PK properties of FBX has been assessed in 19 Phase I studies involving otherwise healthy volunteers (some with co-variables of interest such as renal or hepatic impairment, and older age), 11 drug-drug interaction studies, 3 trials involving subjects with hyperuricaemia and gout, as well as 2 population PK-PD analyses.

The key PK conclusions identified in the submission are as follows:

- Orally administered FBX is rapidly (T_{max} of 1.0-1.5 hours) and well absorbed (at least 84%) from the gastrointestinal tract, but absolute bioavailability has not been determined.
- The proposed commercial formulation and dosage strengths of FBX to be made available in Australia are similar to the 80 mg and 120 mg tablet strengths of the Abbott B1 formulation, which have demonstrated bioequivalence when produced at a commercial scale to the preceding formulations.
- Ingestion of multiple oral doses of FBX 80 mg once daily and single FBX doses of 120 mg following a high fat meal compared to drug administration under fasted conditions, results in a decrease in FBX C_{max} by 38-49%, a decrease in AUC by 16-19%, and a delay in T_{max} by as much as 1 hour.
- The evening administration of FBX results in a slight decrease in C_{max} and a minor delay in T_{max} when compared to morning dose ingestion, however, the total exposure (AUC) to FBX and its metabolites is similar.
- Regarding dose proportionality, the PK parameters of FBX are not time or dose dependent, and remained linear in the dose range of 10-120 mg once daily, but when the dose of FBX exceeds 120 mg/day, a greater than dose proportional increase in AUC was observed, which is postulated to be due to an increase in the extent of enterohepatic recycling of FBX.
- FBX appears to have a low to medium apparent volume of distribution ($\sim 0.7 \text{ L/kg}$).
- FBX is highly bound to human plasma proteins (98-99%; and predominately to albumin), and is constant over the concentration range achieved with FBX 40-120 mg doses. Plasma protein binding of the active metabolites ranges from 82-91%.
- The $T_{1/2}$ of FBX in the plasma ranges from 5 to 8 hours, and reaches steady state within 1 week of once daily dosing.
- FBX is predominately eliminated from the blood by liver metabolism (mainly by metabolism to glucuronide conjugates, and to a much lesser degree by oxidative metabolism), and the majority of metabolites that are eliminated in the urine are not active.
- Subjects with renal impairment have higher unbound FBX AUC_{24} values (~ 1.8 fold increase) than those with normal renal function, but mean FBX T_{max} (0.93-1.33 hours) and unbound

C_{max} values are similar. FBX half-life ($T_{1/2}$) also tended to increase with worsening renal function (4.7 hours in those with normal renal function versus 7.0 hours in subjects with moderate renal impairment). The active metabolites (67M-1, 67M-2 and 67-M4) also showed the same statistically significant relationship between mean AUC_{24} values and worsening CrCl.

- The population PK analyses identified baseline CrCl (both studies), body weight and co-administration of fibrate therapy (Study C##-009 only), as well as smoking status (TMX-##-005 only) as statistically significant covariates for determining FBX clearance.
- The PK of FBX does not appear to be substantially affected by age or gender (when adjusted for body weight).
- Compared to subjects with normal hepatic function, total plasma exposure to FBX is higher in subjects with mild or moderate hepatic impairment (mean FBX unbound C_{max} values 24% higher; and mean unbound AUC_{24} values 24-28% greater); but there are no other observed changes in PK parameters in subjects with hepatic impairment.
- The PK characteristics of FBX in relation to C_{max} and AUC demonstrate relatively low intra-subject and inter-subject variability (though moderate variability for T_{max}), with no observed differences related to FBX formulation or dose across the 20-120 mg range.
- A total of 10 *in vivo* drug-drug interaction studies in humans have been performed. The results indicate that many frequent concomitant medications such as colchicine, indomethacin, hydrochlorothiazide, warfarin, CYP2D6 substrates (desipramine) do not have clinically significant effects on the PK of FBX. However, naproxen (glucuronidation inhibitor) increases exposure to FBX (C_{max} increases by 28%, AUC by 41% and $T_{1/2}$ by 26%). In addition, the concomitant ingestion of antacids has shown to delay the absorption of FBX by ~1 hour, and to cause a decrease in C_{max} of 32%, but no significant change in AUC . The sponsor has not submitted any evaluable data on the potential for interaction between FBX and rosiglitazone (Study TMX-##-103).

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

Table 2 shows the studies relating to each PD topic, and the location of each study summary.

Table 2. Submitted Pharmacodynamic Studies

| PD Topic | Subtopic | Study ID |
|------------------------|---|---|
| Primary Pharmacology | Effect on serum urate concentration, xanthine and hypoxanthine levels; as well as urine uric acid excretion | Healthy Subjects: C##-023, TMX-##-001, TMX-##-008, TMX-##-012 |
| | | Target Population: TMX-##-004 |
| Secondary Pharmacology | Effect on Cardiac QT Interval | C##-023 (Part B) and C##-009 (Sub-study) |
| Gender and Age- | Effect of gender | TMX-##-016 |

| PD Topic | Subtopic | Study ID |
|------------------------------------|-------------------|------------------------------------|
| Related Differences in PD Response | Effect of age | TMX-##-016 |
| PD Interactions | Warfarin | C##-057 and F-P1##-162 |
| | Effect of Food | C##-036 |
| Population PD and PK-PD analyses | Healthy subjects | Nil |
| | Target population | TMX-##-005 and C##-009 (Sub-study) |

One of the PD studies had deficiencies that excluded its results from consideration. Study TMX-##-003 (USA based) was meant to recruit hyperuricaemic subjects with a baseline serum urate level of between 8.0 and 12.0 mg/dL within 6 months of enrolment. However, none of the subjects achieved this target hyperuricaemia level on day -1. In addition, further protocol violations and study conduct irregularities meant the PD data for this study was excluded as it was considered unreliable.

5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional PD studies in humans unless otherwise stated.

5.2.1. Mechanisms of action

FBX is a selective, non-purine inhibitor of XO, which binds very tightly to both the oxidized and reduced forms of XO, reducing the formation of uric acid and therefore lowering serum urate levels. Uric acid is the final product of purine metabolism, and is generated in the pathway of hypoxanthine → xanthine → uric acid. Both steps in this metabolic transformation are catalyzed by XO. FBX blocks the activity of XO through the prevention of substrate binding in a long narrow channel leading to the molybdenum-pterin active site of the enzyme. FBX is not oxidized by XO. The mechanisms of XO inhibition by FBX and allopurinol (active drug, oxipurinol) are different. Allopurinol binds directly to the molybdenum-pterin active site and prevents catalysis. In addition, allopurinol is itself oxidized by XO.

Pharmacodynamic effects

5.2.1.1. Primary pharmacodynamic effects

The primary PD effect of FBX to decrease serum urate (as well as xanthine and hypoxanthine levels) has been demonstrated in both healthy subjects, and in subjects with hyperuricemia and gout. The primary PD effect of FBX in healthy volunteers has been investigated in several Phase I studies: C##-023, TMX-##-001, C##-036 (food effect), TMX-##-008 (renal impairment), TMX-##-012 (hepatic impairment) and TMX -##-016 (gender and age). In the studies involving healthy subjects, the dose-response relationship (percentage change from baseline in serum urate concentration) appeared to be linear for FBX doses ranging from 10 to 120 mg once daily, but the effect appeared to level off for doses above 120 mg. In the healthy volunteer studies, sample sizes ranged from 7 to 18 subjects across the explored doses. Study TMX-##-001 was a placebo-controlled, dose-escalation trial whereby FBX was given at doses ranging from 10-240 mg once daily over 14 days. All of the other Phase I PD studies were open-label. Study C##-23 investigated FBX 300 mg once daily over 7 days, Study C##-036 examined FBX 80 mg once daily (under fasting and fed conditions) in 2 x 6-day periods separated by at least 7 days, while the

other 3 Phase I PD trials (TMX-##-008, TMX-##-012 and TMX-##-016) examined FBX 80 mg once daily over 7 days.

Following multiple daily administrations of FBX 10-300 mg doses in the Phase I studies, mean serum urate concentrations in healthy subjects decreased by approximately 27% - 87% from baseline values (Studies TMX-##-001 and C##-023 Part A). In conjunction with the decreases in serum urate concentrations, there was also a decrease in total daily urinary excretion and urinary concentration of uric acid. Mean serum xanthine concentrations increased following the administration of FBX, and there was also an increase in total daily urinary excretion, urinary concentration, and renal clearance of xanthine. In Study TMX-##-001, serum and urine xanthine levels increased by at least 10-fold from baseline to day 14 (irrespective of FBX dose). Although increased serum xanthine concentrations raise the potential concern of xanthine crystal formation, the concentrations of xanthine observed (for example maximum serum xanthine concentration achieved by any subject in all studies was 1.15 mg/dL – dosed with FBX 300 mg/day) were substantially lower than the solubility limit of xanthine in the serum (that is 10 mg/dL). Unlike serum xanthine concentration, no large increases in serum hypoxanthine concentrations were noted following FBX administration, likely due to the increased renal clearance of hypoxanthine.

In terms of the requested FBX posology of 80 and 120 mg once daily in this submission, the Phase I trials provide some information of relevance. Using a pooled dataset from the Phase I studies, a total of 70 subjects received multiple doses of FBX 80 mg once daily, and this resulted in a mean percentage decrease in serum urate concentrations from baseline of 55.2%. Only 9 healthy subjects (all from Study TMX-##-001) received multiple daily doses of FBX 120 mg, and this resulted in a mean 65.6% reduction in serum urate concentrations from baseline.

In Study TMX-##-008, the mean serum urate concentrations decreased from baseline to day 7 to a similar extent in subjects with normal renal function (58.2% decrease) compared to those with any degree of renal impairment (63.6% reduction in the mild group, 56.7% decrease in the moderate group, and 55.1% reduction in the severe renal impairment subgroup). Expectedly, subjects with greater degrees of renal impairment had higher mean serum urate levels at baseline. Increases in the mean serum xanthine concentrations showed a similar pattern of change in all subgroups (according to baseline level of renal function) over the 7-day study.

In Study TMX-##-012, treatment with FBX 80 mg/day for 7 days resulted in decreases from baseline in the mean serum urate concentrations of 62.5% (from 4.767 mg/dL to 1.830 mg/dL) for subjects with normal liver function, 48.9% (from 4.950 mg/dL to 2.664 mg/dL) for subjects with mild hepatic impairment and 47.8% (5.448 mg/dL to 2.845 mg/dL) for those with a moderate degree of hepatic impairment. Urinary uric acid excretion reduced by 64.0% in subjects with liver function, 62.7% in those with mild hepatic impairment, and 42.7% in the subgroup of subjects with moderate hepatic impairment. The differences in the mean percentage change from baseline in serum urate levels were statistically significant between subjects with normal liver function and those with hepatic impairment (mild and moderate), but the magnitude of the difference is probably not of clinical significance.

In Study C##-036, the administration of FBX 80 mg/day for 6 days under fasting conditions resulted in a greater mean reduction in serum urate concentrations from baseline (58% decrease) compared to when the same treatment was given to the same subjects under fed conditions (51% reduction). The small difference is considered by the sponsor to not be clinically significant, and I concur with that assumption.

The primary PD effect of FBX to lower serum urate concentrations has also been shown in a Phase II, placebo-controlled, dose-finding study (TMX-##-004) which investigated 153 patients (136 male and 17 female) with hyperuricaemia and gout. The 28-day trial examined 3 different daily doses of FBX (40 mg, 80 mg and 120 mg) compared to placebo. In this dose-response study, FBX therapy resulted in a dose-dependent decrease in the mean serum uric acid level,

and a reduction in urinary excretion in urate. At day 28, the mean percentage reduction in serum urate level (enzymatic method) was 2.15% for placebo, 36.6% for FBX 40 mg, 44.3% for FBX 80 mg and 59.1% for FBX 120 mg. In addition, the mean percentage reduction from baseline to day 28 in urine uric acid levels was statistically greater in each of the FBX treatment groups (43.6%-46.5% among the FBX groups) compared to placebo (5.9% reduction from baseline).

Two population PK-PD analyses collected relevant data from target population subjects. In Study TMX-##-005, 88 patients had at least 1 serum sample available for analysis (2 were excluded from analysis), and in the sub-trial of Study C##-009, 125 patients contributed at least 1 serum sample that was included in the PD analysis. In Study C02-009, 13 of 138 subjects in the PD sub-study had their information excluded from the analysis because of outlier values, such as implausibly low values for post-dosing samples. Both population PD models examined the effect of FBX on the baseline serum urate production rate, the elimination rate of urate, and the concentration of FBX at steady state that would result in a 50% decrease in serum urate concentrations from baseline (IC_{50}). Both population PD analyses supported the Phase I study observations in terms of the effect of FBX upon urate production and elimination. In Study TMX-##-005, the estimated population mean for IC_{50} in subjects with gout was 0.209 μ g/mL (95% CI 0.176, 0.242), and the estimated inter-individual variability was 48.4% (95% CI 37.3, 57.4). In Study C##-009, the estimated population mean for IC_{50} in subjects with gout was 0.239 μ g/mL (95% CI 0.193, 0.285), and the estimated inter-individual variability was 66.7% (95% CI 53.4, 77.8). The effects of various covariates on the PD model parameters indicated that only baseline serum urate level had a statistically significant relationship with the baseline rate of urate production. Hence, the reason for inter-individual variability (particularly, IC_{50}) remains unexplained.

5.2.1.2. Secondary pharmacodynamic effects

The effect of FBX on cardiac repolarization as assessed by changes in the QT interval, has been evaluated in both healthy subjects, and in subjects with hyperuricemia and gout.

Part B of Study C##-023 was a Phase I, multicenter, randomized, double-blind trial with a 4-period cross-over design which exposed 44 healthy subjects (32 male, 12 female) to 4 days of once daily therapy with FBX 80 mg, FBX 300 mg, placebo and moxifloxacin 400 mg. Subjects were randomly assigned in equal numbers ($n = 11$) to 1 of 4 treatment sequence regimens. Each subject was to receive all 4 drugs over 4 separate treatment periods. There was a 7-day washout interval between the last dose in each treatment period and the first dose of drug in the subsequent period. The study aimed to evaluate the potential effect of multiple doses of FBX on the QT_c interval (that is prolongation), using moxifloxacin as an active control therapy. Of the 44 enrolled subjects, 43 completed at least 1 treatment period, and 41 completed all 4 periods of the study. Electrocardiographs (ECGs) were taken at day -1, and day 1 through to 4 of each treatment period. The frequency of ECGs was intensive on day -1, day 1 and day 4 (typically, every 15-30 minutes for the first 6 hours post-dosing, and then also at 12 and 24 hours), and on a single occasion (1 hour post-dose) on days 2 and 3. The QT_c interval was quantitatively measured and corrected for using Fridericia's formula (QT_cF). Pair-wise active treatment comparisons versus placebo were made for the effect on QT_c within the framework of an ANOVA model. The number and percentage of subjects with QT intervals classified as normal (≤ 430 msec), borderline (> 430 msec but ≤ 450 msec) or prolonged (> 450 msec) were tabulated using a shift table. In addition, the number and percentage of subjects with increases from baseline in the QT interval (< 30 msec, 30-60 msec, and > 60 msec) were summarized by treatment group. The mean of the maximum post-dose QT_c interval on day 4 was 403.7 msec for FBX 80 mg, 405.1 msec for FBX 300 mg, 415.9 msec for moxifloxacin and 402.9 msec for placebo. The mean of the maximum post-dose QT_c interval for moxifloxacin was statistically greater than placebo ($p < 0.001$) on days 1 and 4, but there were no statistically significant differences between either of the FBX dose regimens and placebo. No subject in any treatment regimen

developed a prolonged QT_c interval (> 450 msec) during the study. The number and percentage of subjects who developed a shift in QT interval from normal to borderline between baseline and day 4 were 2 (5%) for FBX 80 mg, 4 (10%) for FBX 300 mg, 11 (27%) for moxifloxacin and 2 (5%) for placebo. The number and percentage of subjects who developed an increase in QT interval between 30-60 msec from baseline to day 4 were 3 (7%) for FBX 80 mg, 3 (7%) for FBX 300 mg, 19 (46%) for moxifloxacin and 3 (7%) for placebo. In summary, Part B of Study C##-023 showed that FBX in doses up to 300 mg once daily, at steady state, did not cause prolongation in the QT_c interval.

In the Phase III Study C##-009 of 28 weeks duration, a PD sub-study involving 310 patients at selected participating sites underwent serial evaluation of quantitative ECG variables, in particular QT interval (raw value and corrected). ECGs were taken at the baseline and final (week 28) visits, pre-dose, 0.75-2.0 hours post-dose and 2.5-4.0 hours post-dose. There was no significant treatment related (FBX or allopurinol) increase in the frequency of borderline or prolonged QT intervals with therapy compared to the placebo arm.

5.2.1.3. *Time course of pharmacodynamic effects*

In the trials involving healthy volunteers and subjects with hyperuricaemia, steady-state trough serum urate concentrations were generally achieved within the first week of dosing with FBX.

5.2.1.4. *Relationship between drug concentration and pharmacodynamic effects*

As demonstrated in Figure 1, there appears to be a linear dose-response relationship for percentage decrease in serum urate for FBX 10-120 mg (multiple dose administration), which appears to flatten out with FBX doses greater than 120 mg (source: Studies TMX-##-001 and C##-023). Study TMX-##-004 involving subjects with gout supported this early phase trial finding by showing that FBX 40-120 mg/day resulted in a dose-dependent decrease in the mean serum uric acid level (36.6-59.1%), and a reduction in urinary excretion in urate (43.6-46.5%).

5.2.1.5. *Genetic-, gender- and age-related differences in pharmacodynamic response*

There has been no specific study of FBX investigating any potential genetic-related differences in PD response. Potential ethnic differences in the PD (or PK) of FBX have not been reported in this submission. The majority of patients in the FBX clinical study program are of Caucasian background (~80%), but there were subsets of subjects who identified themselves as Asian, Hispanic or other non-Caucasian ethnicity. However, in this submission 5 Phase I studies conducted in Japan, which included limited PD assessments presented in brief reports, were included. Teijin performed these studies in healthy (Studies TMX-##-003, TMX-##-005 and TMX-##-008) and hyperuricaemic Japanese subjects (Studies TMX-##-009 and TMX-##-010). One significant limitation of these studies is that the dose of FBX used was considerably lower (0.2-50 mg) than the requested licensing dose of FBX. Nonetheless, Japanese subjects with hyperuricaemia who received FBX 10, 20 and 40 mg once daily for 2-8 weeks, demonstrated mean decreases from baseline in serum urate concentrations of 20-40%, which is similar to that observed in healthy subjects given the same doses of FBX in the Phase I studies performed in the USA (Study TMX-##-001).

Study TMX-##-016 was an open-label, parallel-group Phase I trial, which examined the effect of gender and age on the PD of FBX 80 mg once daily, administered for 7 consecutive days. Female subjects (n = 24) showed a statistically greater mean decrease at 7 days from baseline in serum urate levels (59% reduction) compared with otherwise healthy male volunteers (n = 24; 52% reduction), but the decrease is unlikely to be of clinical relevance. The result could not be accounted for by differences between the genders in body weight and drug AUC. There were no gender related differences for the decreases in urinary uric acid excretion, increases in serum and urinary xanthine levels, and increased hypoxanthine levels. In addition, age (18-40 years of age [n = 24] versus ≥ 65 years [n = 24]) did not appear to influence the PD effects of FBX in a statistically significant manner.

5.2.1.6. *Pharmacodynamic interactions*

No study of FBX concurrently administered with allopurinol has been undertaken. FBX drug interaction studies with azathioprine and mercaptopurine have not been performed. However, based on the mechanism of action of XO inhibition, co-administration of FBX with azathioprine or mercaptopurine is not recommended.

Two drug-drug interaction studies (C##-057 and F-P1##-162) involving healthy subjects have demonstrated that multiple doses of FBX have no clinically significant effects on the PD of concomitantly administered warfarin. Both studies were of similar design, and demonstrated that multiple oral doses of FBX 80 mg and 120 mg had no effect on the PD of warfarin as measured by the maximum INR, 24-hour mean INR, and 24-hour mean Factor VII values. These studies support the recommendation that no dose adjustment is necessary for warfarin when it is co-administered with FBX.

5.3. **Evaluator's overall conclusions on pharmacodynamics**

In this submission, the PD properties of FBX have been assessed in at least 6 Phase I studies involving otherwise healthy volunteers (some with co-variables of interest such as renal or hepatic impairment, and older age), as well as 3 trials involving subjects with hyperuricaemia and gout (including 2 population PK-PD analyses).

The key PD conclusions identified in the submission are as follows:

- Following administration of multiple once daily oral doses of FBX 80 and 120 mg for 7 days, mean serum urate concentrations reduce by a mean of 55-66% from baseline.
- There is a linear dose-response relationship for FBX doses 10-120 mg, which appears to level off for doses > 120 mg.
- When FBX is administered in the fasted versus fed state, there is a slightly greater reduction in serum urate concentrations at 7 days, but this difference is unlikely to be of clinical relevance.
- The percentage reduction in serum urate concentrations following ingestion of FBX is unaffected by age, or presence of renal impairment.
- The percentage reduction in serum urate concentrations following administration of FBX is greater in females versus male subjects, and higher in those with normal liver function versus subjects with mild-moderate hepatic impairment, but the changes are of small magnitude and therefore unlikely to be of clinical significance.
- Steady state serum urate concentrations are achieved within the first week of multiple once daily dosing with FBX.
- Mean serum xanthine concentrations increase significantly following multiple daily doses of FBX, especially in subjects with renal impairment, but the concentrations reached are substantially lower than the solubility limit in serum (that is unlikely to form xanthine crystals).
- Consistent with the serum changes, there are decreases in urinary excretion of uric acid and an increase in urinary excretion of xanthine. Serum hypoxanthine levels do not significantly increase due to increased urinary elimination of this compound.
- Two population PD analyses (Studies TMX-##-005 and C##-009) demonstrate moderate inter-individual variability for the concentration of FBX at steady state that would result in a 50% decrease in serum urate concentrations from baseline (IC_{50}), which remains unexplained.

- FBX in doses up to 300 mg/day at steady state does not cause any significant effects on cardiac repolarization such as prolongation of the QT interval in normal healthy subjects (Part B of Study C##-023), as well as patients with gout (Study C##-009).
- Two drug-drug interaction studies (C##-057 and F-P1##-162) involving healthy subjects have demonstrated that multiple doses of FBX have no clinically significant effects on the PD of concomitantly administered warfarin.

6. Dosage selection for the pivotal studies

Study TMX-##-004 was a Phase II, dose-finding trial, which informed the selection of FBX doses (80 and 120 mg once daily) chosen for examination in the 2 pivotal Phase III studies (C##-009 and C##-010). After 28 days of treatment, the mean percentage reduction in serum urate level (by enzymatic method) was 2.15% for placebo, 36.6% for FBX 40 mg/day, 44.3% for FBX 80 mg/day and 59.1% for FBX 120 mg/day. In addition, the proportion of hyperuricaemic patients achieving a serum urate level of < 6.0 mg/dL (by enzymatic method) in Study TMX-##-004 was greater in each of the FBX treatment groups (55.9% [19/34] in those treated with FBX 40 mg/day, 75.7% [28/37] for FBX 80 mg/day and 94.1% [32/34] for patients receiving FBX 120 mg/day) compared to zero patients who received placebo therapy. In Study C##-009, a FBX 240 mg/day arm was included to provide additional safety information on twice the maximal intended dose of FBX for registration (that is FBX 120 mg/day). FBX 240 mg/day was administered to healthy volunteers for 14 days in the Phase I Study TMX-##-001, and was generally well tolerated. In Study C##-010, only 2 doses of FBX were investigated (80 and 120 mg/day). The third Phase III trial (Study F-GT##-153) post-dated the 2 pivotal Phase III studies, and at the request of the FDA assessed the lower dose of FBX 40 mg/day, as this dose had not been investigated in either of the preceding Phase III studies.

The doses of allopurinol used in the Phase III trials as the active treatment comparator for FBX were acceptable. At the time when the 2 pivotal Phase III studies (C##-009 and C##-010) were performed, it was recommended that the dose of allopurinol be reduced from 300 mg/day (in those with normal function) to 100 mg/day in patients with renal impairment. In the subsequent Phase III Study (F-GT##-153) the comparator doses of allopurinol were adjusted to contemporary practice guidelines – a minimum of 300 mg/day for those with CrCl of at least 60 mL/min; and 200 mg/day for patients with CrCl 30-59 mL/min.

The use of NSAID and colchicine for gout flare prophylaxis, and treatment of acute gouty arthritis attacks, is consistent with contemporary clinical practice in Australia. It is also acceptable to use low dose oral prednisone (< 10 mg/day) in selected patients with difficult to control gouty arthritis in the setting of co-morbidities such as renal impairment and/or age > 65 years, which limit alternative treatment options (NSAID and colchicine). However, the exclusion of subjects who were taking concurrent clopidogrel from the Phase III Study F-GT##-153 limits the external validity of the studied populations. Concurrent cardiovascular disease requiring anti-platelet therapy (other than low dose aspirin) is relatively common in the intended target population. The 2 pivotal Phase III studies (C##-009 and C##-010) did not specify in their protocols, or report data, on whether or not anti-platelet drugs (other than low dose aspirin) were allowed or actually taken.

7. Clinical efficacy

7.1. The sponsor proposes the indication: 'Treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history of, or presence of, tophus and/or gouty arthritis). ADENURIC is indicated in adults'.

7.1.1. Pivotal efficacy studies

7.1.1.1. Study C##-009

7.1.1.1.1. Study design, objectives, locations and dates

Study C##-009 was a Phase III, randomised, parallel-group, active (allopurinol) and placebo controlled study with 5 treatment groups (placebo, FBX 80 mg once daily, FBX 120 mg once daily, FBX 240 mg once daily, or allopurinol 300 mg/day for subjects with serum creatinine of equal to or less than 1.5 mg/dL at baseline; or allopurinol 100 mg/day for subjects with baseline serum creatinine between 1.5 and 2.0 mg/dL). It had a 28-week, double-blind treatment period. The primary objective of the trial was to compare the efficacy and safety of different oral doses of FBX versus placebo and allopurinol in subjects with gout. The FBX 240 mg dose arm was primarily included to provide safety data on twice the maximum daily dose intended for registration.

The study consisted of a wash-out/run-in period that included a screening visit (day -14 for patients who were taking allopurinol or uricosuric drugs prior to the study, or day -4 for subjects not taking such medicines prior to the trial), a day -4 visit for subjects whose screening visit occurred on day -14, a day -2 visit, and day 1 visit, followed by a 28 week, double-blind treatment phase. Subjects who completed the 28-week, double-blind phase were given the option of enrolling into a 24 month, open-label extension study with FBX (C##-021). The 14-day wash-out period for allopurinol and uricosuric drugs is sufficient to limit any ongoing efficacy of these medicines on the study endpoints. The doses of allopurinol used were selected by the dosing information in the USA allopurinol product information (PI) at the time the trial was planned.

In Study C##-009, the first subject was dosed on 21 February, 2003 and the last subject procedure occurred on 7 April, 2004. A total of 167 centres, all located in the USA, recruited patients. There were 3 amendments to the original protocol, the latter 2 occurring after the commencement of patient recruitment. The amendments contained clarifications about the statistical analysis plan, and adding the procurement of serial ECGs to the PK/PD sub-study. None of the amendments resulted in major changes to the study design, which may have affected the outcome or statistical analysis.

7.1.1.1.1.2. Inclusion and exclusion criteria

To be eligible for inclusion, patients had to be between 18 and 85 years of age with hyperuricaemia (defined as a serum urate level of at least 8.0 mg/dL at the day -2 visit), and a history or presence of gout as defined by preliminary criteria of the ACR (American Rheumatism Association) for the classification of the acute arthritis of primary gout (Ref). At the request of the FDA, at least 30% of the subjects were to have a day -2 serum urate level of at least 10.0 mg/dL. Subjects were also required to have normal renal function at baseline, defined as a serum creatinine of 2.0 mg/dL or less, and a creatinine clearance of at least 20 mL/min (calculated by Cockcroft and Gault formula).

The exclusion criteria involved 5 domains and patients meeting any 1 of the criterion were excluded.

- Diagnosis – xanthinuria, secondary hyperuricaemia, and pregnancy/lactation;

- Past history – renal calculi, alcohol abuse within 5 years (defined as those consuming 14 or more standard drinks/week), intolerant of allopurinol, unable to take gout flare prophylaxis medication (naproxen or colchicine) due to intolerance, rheumatoid arthritis, active peptic ulcer, and malignancy within the last 5 years (except basal cell skin cancer of the skin);
- Baseline results – hepatic dysfunction (defined as ALT or AST > 1.5 upper limit of normal [ULN]), or renal impairment (defined as serum creatinine > 2.0 mg/dL);
- Concurrent treatments – use of thiazide diuretic therapy, aspirin > 325 mg/day, oral prednisone > 10 mg/day (inhaled and intranasal corticosteroids were allowed), change in oral contraceptive treatment or hormone replacement therapy in the last 3 months, and concomitant urate lowering therapy.

7.1.1.3. *Study treatments*

Subjects were randomized in a 1:2:2:1:2 ratio to receive placebo, FBX 80 mg once daily, FBX 120 mg once daily, FBX 240 mg once daily or allopurinol (300 mg/daily for subjects with serum creatinine < 1.5 mg/dL on day -2, or 100 mg/daily for subjects with serum creatinine > 1.5 mg/dL and < 2.0 mg/dL on day -2). Subjects with a serum creatinine > 2.0mg/dL at either the screening, day -4 or day -2 visits were not eligible for randomization.

Subjects taking allopurinol or uricosuric agents prior to the study discontinued them at the day -14 screening visit. These subjects began gout prophylaxis medicines at the screening visit (day -14) consisting of naproxen 250 mg twice daily or colchicine 0.6 mg once daily, and continued taking the medication through to the week 8 visit. Subjects who were not taking uricosuric agents or allopurinol prior to the study did not require a washout period, and did not require naproxen or colchicine prior to day 1. These subjects began prophylaxis (naproxen 250mg twice daily or colchicine 0.6 mg/day) at the day 1 visit and continued them through to week 8. Across the 5 treatment groups, 50-60% used prophylactic colchicine and 40-49% used prophylactic naproxen, for a mean number of 56-60 days. There were no statistically significant differences between the treatment groups with respect to the incidence, type and duration of prophylactic medicine use. Up to 40% of patients required adjustment to their gout prophylaxis (increase or decrease dosage, or a switch to alternative treatment) during the first 8 weeks, and less than 25% discontinued gout prophylaxis before 8 weeks.

If an acute gout attack occurred during the 14-day washout /run-in period, or during the first 8 weeks of the 28-week double-blind treatment period, subjects taking naproxen 250 mg twice daily were allowed to take an additional 250 mg for 1 or 2 days, and subjects taking colchicine 0.6 mg/day were allowed to take an additional 0.6 mg tablet for 1 or 2 days. Subjects who experienced a gout flare on day 1 were not to be randomised until the gout flare resolved.

At the week 8 visit, the investigator provided subjects with a prescription for anti-inflammatory or analgesic medicines of their own choosing (NSAID [for example indomethacin, naproxen, ibuprofen, sulindac, ketoprofen], pain medications [for example paracetamol], corticosteroids or colchicine) to be used in the event the subject had a flare during the remainder of the study. Paracetamol and non-salicylate NSAIDs were all allowed on an as needed basis for treating gout flare.

7.1.1.4. *Efficacy variables and outcomes*

The primary efficacy outcome in Study C##-009 was the proportion of subjects whose last 3 serum urate levels were < 6.0 mg/dL. Serum urate levels were assessed at each visit in the wash-out/run-in period, day 1, and weeks 2, 4, 6, 8, 12, 16, 20, 24 and 28. The 2006 EULAR evidence-based recommendations for gout management state that maintaining a serum urate level below the saturation point for monosodium urate crystal deposition (6.0mg/dL, or 360 μ mol/L) has been recommended for the treatment of gout (Zhang et al, 2006). The supporting literature identifies that a sustained reduction of serum urate to < 6.0 mg/dL is correlated with reduced urate crystals in synovial fluid, a reduction in tophi size, and a lower frequency of gouty

attacks over time (Khanna et al, 2012). In Study C##-009 a central laboratory using a validated enzymatic method measured serum urate levels.

Subjects were assessed at screening for the presence and number of palpable gouty tophi. In a subset of subjects identified to have a primary palpable tophus (> 10 mm in diameter) at the screening visit, the percentage reduction in primary tophus size, as determined by physical measurement, was a secondary efficacy endpoint. The tophus was measured during the active treatment period every 4 weeks (that is week 4 through to week 28). The physical measurement technique had a reproducible and consistent methodology.

Various Quality of Life (QOL) instruments such as the SF-36 scale, the Medical Outcomes Study (MOS) Health Distress Scale and the Gout Assessment Questionnaire (GAQ) were collected during the study. The SF-36 scale is a validated 36-item QOL tool encompassing 8 general health concepts with demonstrated reliability in general and ambulatory populations, and in populations with chronic disease. The MOS Health Distress Scale is a 6-item measure that focuses on psychological distress attributed to health problems. The GAQ is a new QOL tool, developed by the study sponsor, which assesses a variety of gout-specific aspects of health (in 8 domains) including pain, well-being, productivity, and treatment satisfaction. The GAQ scale was developed from analyses using the combined data from Study TMX-##-004 and the first year of Study TMX-##-005. The results of these analyses suggest that the GAQ has acceptable validity and reliability in an adult population suffering from gout.

Other secondary efficacy outcomes included:

- Proportion of subjects whose serum urate levels were < 6.0 mg/dL at each study visit,
- Proportion of subjects whose serum urate levels were < 5.0 mg/dL and < 4.0 mg/dL at week 28,
- Mean percentage reduction in serum urate levels from baseline to week 28,
- Proportion of subjects requiring treatment for a gout flare between weeks 1 to 8, 8 to 28 and overall,
- Mean percentage reduction in primary tophus size in subjects with a palpable tophus at screening, and
- Mean reduction in the total number of tophi in the subset of patients with a palpable tophus at screening.

7.1.1.1.5. *Randomisation and blinding methods*

Randomization was computer generated and done at a central facility (IVRS). The randomization code was maintained in a locked, confidential location until the time of un-blinding by the study statistician. Subjects were stratified according to renal function at baseline: no renal impairment (day -2 serum creatinine < 1.5 mg/dL) or renal impairment (day -2 serum creatinine > 1.5 mg/dL but < 2.0 mg/dL). The 2 groups were randomly assigned separately by IVRS, so that all 5 of the treatment groups were balanced with respect to the number of patients with normal or impaired renal function at baseline.

All study medicines were blinded with de-identified and matching placebo therapies. Each subject was asked to take 2 small tablets, 2 large tablets and 1 capsule, together in the morning, which provided a treatment of placebo, FBX or allopurinol. Medicines were supplied in blister cards (FBX) and bottles (allopurinol).

7.1.1.1.6. *Analysis populations*

All efficacy analyses (primary and secondary endpoints) were performed on the Intention-to-Treat (ITT) population, except for the secondary analyses of the percentage reduction in primary tophus size and the reduction in the total number of tophi. These secondary analyses

were only performed on the subset of patients with a documented primary tophus at baseline. The ITT population was defined as all randomized subjects who received at least 1 dose of study drug and who had serum urate level > 8.0 mg/dL at the last visit prior to day 1.

7.1.1.7. *Sample size*

It was planned that a total of 1000 subjects (125 subjects in each of the placebo and FBX 240 mg once daily treatment groups; and 250 subjects in each of the FBX 80 mg and 120mg once daily, and allopurinol 300/100mg treatment groups were planned to be enrolled in the study). The treatment group randomization ratio was chosen because a larger number of subjects were required to show non-inferiority between the FBX 80mg and 120mg treatment groups versus the allopurinol 300/100mg treatment group, than was required to detect a difference between the placebo treatment group and the FBX treatment groups. For the determination of non-inferiority between each of the FBX treatment groups (80 mg and 120 mg) and the allopurinol treatment arm, it was anticipated that the response rate of 60% was to be expected in the allopurinol treatment group, and at least 64% for the FBX treatment groups. These assumptions were based on the results of Study TMX-##-004 and a literature review of the allopurinol response data (proportion of patients achieving a single serum urate level of < 0.6 mg/dL after 4 weeks of therapy). The sample size of 1000 subjects was to provide:

- at least 95% power to detect a difference of 45% between each of the FBX treatment groups and placebo for the primary efficacy outcome,
- at least 80% power to meet the non-inferiority criteria between at least 1 FBX treatment group and the allopurinol arm for the primary efficacy variable, and
- at least 90% power to detect a 15% difference between a FBX treatment group and the allopurinol 300/100 mg arm for the primary efficacy outcome. However, the FBX 240mg treatment group was included in this study to establish a drug safety profile at a dose twice the anticipated maximum clinical dose of 120 mg/day, and therefore comparisons between the FBX 240 mg treatment group and the allopurinol treatment group were not powered.

7.1.1.8. *Statistical methods*

The comparisons for the primary efficacy variable (proportion of patients with last 3 urate levels < 6.0 mg/dL) were done sequentially using a closed testing procedure within each of 3 steps. The first step involved comparing each FBX treatment group to placebo (stratified by baseline renal function) to test for superiority. Superiority of a FBX treatment group to placebo was declared if the p-value from the CMH test was less than or equal to the critical significance level based on Hochberg's method. If each dose of FBX was shown to be superior to placebo, the analysis proceeded to step 2. In the second step, the FBX 80 mg and 120 mg treatment groups were compared to allopurinol for non-inferiority. Non-inferiority to allopurinol was declared if the absolute value of the lower bound of the 97.5% CI did not exceed 10%. In the third step, each FBX treatment group (80 mg and 120 mg) shown previously to be non-inferior to allopurinol was then tested for superiority to allopurinol. The overall 0.05 alpha level was maintained by using binomial 97.5% Confidence Intervals (CI) for the non-inferiority tests, and Hochberg's method for the superiority testing. Pair-wise comparisons between all treatment groups were made with Fisher's exact test. A sensitivity analysis was conducted for the primary efficacy outcome by using the available (1 or 2) serum urate levels to determine response for subjects who prematurely discontinued (these subjects were assigned non-responder status in the primary analysis). The effect of various patient factors (age, gender, ethnicity, baseline BMI, alcohol use, compliance, baseline serum creatinine, use of previous urate lowering therapy, baseline serum urate levels, and presence of baseline palpable tophus) on the primary outcome measure was also assessed.

For the secondary efficacy measures, pair-wise comparisons between all treatment groups were made using Fisher's exact test for the proportion of patients whose serum urate levels were <

6.0 mg/dL and the proportion of subjects requiring treatment for a gout flare; Analysis of Variance (ANOVA) was used for the percentage reduction in serum urate levels and QOL tools; and the Wilcoxon rank-sum test was employed for the percentage reduction in primary tophus size and the reduction in the total number of tophi. No adjustments were made to the overall 0.05 alpha level for the secondary efficacy variables.

7.1.1.9. Participant flow

A total of 1072 subjects were randomized and received at least 1 dose of study drug in Study C02-009: 134 subjects received placebo, 267 received FBX 80 mg/day, 269 received FBX 120 mg daily, 134 received FBX 240 mg/day, and 268 received allopurinol (300 mg [n = 258] or 100 mg daily [n = 10]). Five randomized subjects, all of whom were allocated to the FBX 80 mg/day group, were excluded from the ITT analysis because their serum urate level at the last visit prior to day 1 was < 8.0 mg/dL. In addition, 2 patients (1 in the FBX 80 mg group and another in the allopurinol arm) were excluded from the clinical trial database as the recruitment site was closed due to GCP non-compliance.

Overall, 28% (300/1072) of subjects prematurely discontinued treatment in Study C##-009: 24.6% (33/134) of subjects in the placebo group, 34.8% (93/267) subjects in the FBX 80mg/day group, 25.7% (69/269) subjects in the FBX 120 mg/day group, 35.8% (48/134) subjects in the FBX 240 mg arm, and 21.3% (57/268) subjects in the allopurinol arm. Of the subjects who prematurely discontinued, 62.7% (188/300) discontinued within the first 12 weeks, and discontinuation rates declined thereafter. The percentage of subjects who prematurely discontinued within the first 12 weeks was comparable across the treatment groups (ranging from 58% to 69%). The most common reason for discontinuation from the study was lost to follow-up (24.0%; 72/300). A greater proportion of subjects in the FBX treatment groups (14.0% [13/93] for FBX 80 mg, 8.7% [6/69] for FBX 120 mg, and 16.7% [8/48] for FBX 240 mg) discontinued due to gout flare compared with the placebo (0 patients) and allopurinol treated subjects (1.8%; 1/57).

7.1.1.10. Major protocol violations/ deviations

A total of 89 subjects had deviations from the admission criteria for the study: 11 placebo patients, 26 subjects in the FBX 80 mg group, 22 in the FBX 120 mg arm, 11 in the FBX 240 mg group, and 19 subjects in the allopurinol cohort. Nine of these subjects (1 placebo, 3 FBX 80 mg, 2 FBX 120 mg, 1 FBX 240 mg and 2 allopurinol subjects were prematurely discontinued, at the request of the study sponsor, due to admission criteria violations. The most common admission criteria violations in descending order of occurrence was subjects with a history of renal calculi being enrolled (n = 17), concomitant thiazide diuretic therapy at baseline (n = 15), subjects whose alcohol intake was > 14 drinks/week (n = 15), active liver disease or hepatic dysfunction at screening (n = 12), impaired renal function at baseline (n = 8), and serum urate level of < 8.0 mg/dL at the screening (n = 6). Protocol deviations at baseline were equally distributed between the treatment groups.

During the study, a total of 14 subjects received the wrong study drug treatment at some point in the trial: 5 in the FBX 80 mg group, 6 in the FBX 120 mg arm, 1 in the FBX 240 mg cohort, and 2 in the allopurinol group. Regarding prohibited concomitant medication use during the study, a noteworthy proportion of subjects in all treatment groups received prednisone > 10 mg/day: 15.7% (21/134) for placebo, 15.8% (42/267) for FBX 80 mg, 13.4% (36/269) for FBX 120 mg, and 19.4% (26/134) for the allopurinol group.

7.1.1.11. Baseline data

No clinically relevant differences were observed across the treatment groups for any demographic or baseline disease characteristic of interest. There were no statistically significant differences among the treatment groups in gender, race, age, height, tobacco use, alcohol use or BMI. A statistically significant difference was observed among the treatment groups in weight, with a lower mean weight in the placebo group (215.2 pounds) compared to the FBX 80 mg

group (227.6 pounds), FBX 120 mg arm (230.3 pounds), FBX 240 mg group (227.2 pounds) and allopurinol treatment group (225.8 pounds). Subjects ranged in age from 22 to 84 years. The mean age ranged from 50.6 to 54.3 years among all treatment groups. The majority of subjects were Caucasian (78%) and most subjects were male (94%). The majority of subjects reported the use of alcohol (66%) and were non-/ex-tobacco users (80%). The mean BMI for all subjects was 32.7 kg/m², and 62% had a BMI of > 30 kg/m².

A statistically significant difference was observed among the treatment groups for the proportion of subjects using regular low-dose aspirin at baseline. A greater proportion of subjects in the placebo and FBX 240 mg treatment groups were taking low-dose aspirin at baseline (22% and 25%, respectively) compared to subjects in the FBX 80 mg, FBX 120 mg and allopurinol treatment groups (17%, 14% and 13% respectively). No other statistically significant differences were observed for any concurrent medications or relevant past medical history at baseline. Almost half of all subjects had a history of hypertension (46.8%; 502/1072), and one third (32.6%; 349/1072) had hyperlipidaemia. A total of 30 subjects (2.8% of 1072) had a history of congestive cardiac failure. Moreover, 13.4% (144/1072) of all subjects had a history of cardiovascular disease, and 8.4% (90/1072) had diabetes.

There was no statistically significant difference among the treatment groups at baseline in any gout history variable or mean baseline serum urate level.

The mean number of years with gout ranged from 9.9 to 11.8 years across all treatment groups. The majority of subjects in each treatment group experienced their last gout flare within 1 year of enrolment (> 87%). Overall, 20% (219/1072) of subjects had a primary palpable tophus at screening, with an average of 5.7 years since the onset of the first tophus. The most common locations for the tophi were ankle/foot (including the toe and instep), elbow, and wrist/hand.

Mean serum urate levels at baseline ranged from 9.78 to 9.96 mg/dL across all treatment groups, and 39% of all subjects had a baseline serum urate level > 10.0 mg/dL. Across all treatment groups, the most frequently occurring baseline serum urate level was between 9.0 and < 10.0 mg/dL.

7.1.1.1.12. *Results for the primary efficacy outcome*

The proportion of subjects whose last 3 serum urate levels were < 6.0 mg/dL were 0% in the placebo group, 48.1% (126/262) in the FBX 80 mg arm, 65.1% (175/269) in the FBX 120 mg group, 68.7% (92/134) in the FBX 240 mg cohort, and 22.4% (60/268) in the allopurinol group. Each of the FBX treatment groups and the allopurinol therapy arm were statistically superior to placebo. The 97.5% CIs for the differences in response rates between FBX 80 mg versus allopurinol were 16.7%-34.7% (p < 0.001); and for FBX 120 mg versus allopurinol were 34.0%-51.3% (p < 0.001), thus demonstrating the non-inferiority of both FBX 80 mg/day and 120 mg/day relative to allopurinol 300/100 mg daily.

On further analysis, the differences between the FBX 80 mg and 120 mg groups versus allopurinol confirmed that each FBX dose was statistically superior to allopurinol. The difference between the FBX 240 mg arm and the allopurinol treatment group was also statistically significant. Furthermore, the difference between the FBX 80 mg treatment group and each of the other FBX treatment groups was statistically significant. The difference between the FBX 120 mg and 240 mg treatment groups was not statistically significant.

For subjects who prematurely discontinued before at least 3 serum urate levels were obtained, a sensitivity analysis was conducted for the primary efficacy outcome using the available (1 or 2) serum urate levels to determine response. In the primary analysis these subjects were assigned non-responder status. In all of the active treatment groups the proportions of subjects whose last 3 serum urate levels were < 6.0 mg/dL were slightly higher in this sensitivity analysis compared to the overall analysis. Among ITT subjects, response rates were 0% in the placebo group, 57% in FBX 80 mg arm, 70% in the FBX 120 mg group, 83% in the FBX 240 mg group, and 25% in the allopurinol treatment group. The differences between each of the active

treatment groups and placebo were statistically significant ($p < 0.001$). The 97.5% CIs for the differences in response rates confirmed the non-inferiority of FBX 80 mg and 120 mg compared to allopurinol. Also, the differences between each of the FBX treatment groups and the allopurinol arm confirmed that each dose of FBX was statistically superior to allopurinol ($p < 0.001$).

The response rates were also evaluated in subjects with renal impairment. However, there were only a small number of subjects ($n = 40$) who were randomized with serum creatinine levels $> 1.5\text{mg/dL}$. In the renal impairment group, the target serum urate response rate was 0% (0/5) in the placebo arm, 44% (4/9) in the FBX 80 mg group, 45% (5/11) in the FBX 120 mg cohort, 60% (3/5) in the FBX 240 mg group, and 0% (0/10) in the allopurinol 100 mg/day patients.

Response rates were compared using CMH methodology adjusting for gender, age, race, overall compliance, baseline measured creatinine clearance, baseline serum urate level, baseline palpable tophus presence, previous use of urate-lowering therapy, history of cardiovascular risk factors, alcohol use, baseline BMI, use of low-dose aspirin, tobacco use, and presence of metabolic syndrome. After adjusting for each factor, statistically pair-wise differences were observed between each of the active treatment groups and the placebo arm, with higher response rates in the active treatment groups ($p < 0.01$). Higher response rates were also observed in the FBX treatment groups compared to the allopurinol-treated subjects ($p < 0.01$). The difference between the FBX 80 mg group and each of the other FBX treatment groups was also statistically significant ($p < 0.01$) after adjusting for each factor.

Among the subset of subjects with a palpable tophus at baseline, response rates were statistically lower (22%) in the allopurinol treatment group compared to each FBX arm (37% for 80 mg, 55% for 120 mg, and 65% for 240 mg). All active treatment groups demonstrated statistically significant higher response rates than the placebo group (0%). Both the FBX 120 mg and 240 mg treatment groups demonstrated a statistically higher response rate than FBX 80 mg in this subset of patients.

After adjusting for serum urate level at baseline, target serum urate response rates were lower in each of the active treatment groups (allopurinol and FBX) if the baseline serum level exceeded 10.0 mg/dL. All active treatment groups demonstrated statistically significantly higher response rates than the placebo group (0%). Each of the FBX treatment groups demonstrated superiority to allopurinol therapy, however, the FBX 120 mg and 240 mg groups also demonstrated statistically higher response rates than the FBX 80 mg group.

7.1.1.2. *Results for other efficacy outcomes*

7.1.1.2.1. *Proportion of subjects whose serum urate levels were $< 6.0\text{mg/dL}$ at each visit*

At each scheduled visit up to 28 weeks, the proportions of subjects whose serum urate levels were $< 6.0\text{mg/dL}$ were numerically higher and reached statistical significance in each of the FBX treatment groups compared to allopurinol therapy; and in each of the 4 active treatment groups compared to placebo. A reduction in serum urate levels to $< 6.0\text{mg/dL}$ was observed in all treatment groups at the week 2 visit and was maintained throughout the 28 week treatment period. Over the course of the study, response rates ranged from 0-1% in the placebo group, 69-80% in the FBX 80 mg group, 79-89% in the FBX 120 mg arm, 85-98% in the FBX 240 mg cohort, and 35-41% in the allopurinol treatment group. The expected 60% response rate (as expected in the sample size calculations) in the allopurinol treatment group was not seen in any cohort of allopurinol treated subjects, even those with a lower baseline serum urate level (that is $< 9.0\text{ mg/dL}$).

7.1.1.2.2. *Proportion of subjects whose serum urate levels were < 5.0 mg/dL and < 4.0 mg/dL*

At week 28, the proportions of subjects whose serum urate levels were < 5.0 mg/dL were statistically greater in each of the FBX treatment groups compared to allopurinol; and in each of the 4 active treatment groups compared to placebo.

The proportion of subjects with serum urate levels < 5.0 mg/dL at week 28 was 0% for placebo, 51% (82/161) for FBX 80 mg, 72% (135/188) for FBX 120 mg, 87% (72/83) for FBX 240 mg, and 13% (28/208) in the allopurinol treatment group. Furthermore, the proportions of subjects with serum urate levels < 5.0 mg/dL at the week 28 or final visit was numerically higher with increasing FBX dose.

The proportions of subjects whose serum urate levels were < 4.0 mg/dL were statistically greater in each of the FBX treatment groups compared to the allopurinol arm; and in each of the FBX therapy groups compared to placebo at week 28 and final visits. At week 28, the proportion of subjects whose serum urate levels were < 4.0 mg/dL ranged from 0% for the placebo group, 21% (34/161) in the FBX 80 mg, 41% (77/188) in the FBX 120 mg arm, 78% (65/83) in the FBX 240 mg group and 2% (5/208) in the allopurinol treatment group.

7.1.1.2.3. *Mean percentage reduction in serum urate levels*

The mean percentage changes from baseline in serum urate levels were statistically higher in each of the FBX treatment groups compared to the allopurinol treated subjects. In addition, at weeks 28 and 52, as well as the final recorded visit, a statistically greater mean change in serum urate levels was observed in the patients who received FBX 120 mg/day versus those who took FBX 80 mg/day.

7.1.1.2.4. *Percentage reduction in primary tophus size*

A total of 217 subjects (20.2% of 1072) had a primary tophus at baseline: 29 in the placebo group, 46 in the FBX 80 mg arm, 53 in the FBX 120 mg group, 25 in the FBX 240 mg cohort and 64 subjects in the allopurinol group. Due to protocol specified unequal randomization, the placebo and FBX 240 mg treatment groups enrolled only half as many subjects as the other groups. Among subjects with a primary tophus at baseline, there were no statistically significant differences between any of the 5 treatment groups for the percentage changes from baseline in primary tophus size at the week 28 (or final visit). In each treatment group, there was a trend towards median percentage reductions from baseline over time. The median percentage reduction from baseline to week 28 was 52% in the placebo group, 45.6% in the FBX 80 mg arm, 54.2% in the FBX 120 mg group, 53.2% in the FBX 240 mg cohort and 31.5% in the allopurinol treatment group.

An additional analysis of the percentage reduction in primary tophus size excluding elbow locations was performed. Elbow tophi were excluded due to variability in measurements at that site, possibly due to olecranon bursal fluid. Among subjects with a primary palpable tophus at baseline, the percentage change in primary tophus size (excluding elbow locations) was statistically different between the FBX 120 mg and allopurinol treatment groups at week 28. The median percentage reduction from baseline to week 28 was 39.6% in the placebo group, 33.2% in the FBX 80 mg arm, 56.7% in the FBX 120 mg group, 44.3% in the FBX 240 mg cohort and 16.1% in the allopurinol treatment group.

Among subjects with a primary palpable tophus at baseline, the median percentage change from baseline in primary tophus size was numerically greater in the group that achieved an average post-baseline serum urate level < 6.0 mg/dL (n = 107) compared to those who didn't achieve that target serum urate level (n = 100). At week 28, the median percentage reduction from baseline in the primary tophus size was 51.4% in the group of subjects that achieved an average post-baseline serum urate level < 6.0 mg/dL compared to 39.0% in the group of subjects that achieved an average post-baseline serum urate level > 6.0 mg/dL. Among the 207 subjects with

a primary palpable tophus at baseline and at least 1 post-baseline serum urate level, the number of subjects with an average post-baseline serum urate level < 6.0 mg/dL was greater in the FBX 120 mg treatment group (40 subjects) compared to the placebo (0 patients), FBX 80 mg (23 patients), FBX 240 mg (22 subjects) and allopurinol treatment groups (22 subjects).

7.1.1.2.5. *Reduction in total number of tophi*

There were no statistically significant differences between treatment groups in the change from baseline in number of tophi at the week 28 visit, with the exception of the difference between FBX 120 mg and placebo. In each treatment group, there was little change in median values over time, which probably reflects the 28-week treatment follow-up period being too short to accurately assess this endpoint. A decrease in the mean number of tophi was noted in each treatment group and the mean change from baseline to week 28 was -0.3 tophi in the placebo group, -0.3 in the FBX 80 mg arm, -1.2 in the FBX 120 mg cohort, -0.4 in the FBX 240 mg group and -0.4 tophi in the allopurinol treatment group.

7.1.1.2.6. *Proportion of subjects requiring treatment for gout flare*

The majority of subjects in all treatment groups received treatment for a gout flare during the study: 55% (74/134) for the placebo group, 57% (149/262) for the FBX 80 mg arm, 62% (168/269) for the FBX 120 mg group, 66% (89/134) for the FBX 240 mg cohort and 51% (136/268) for the allopurinol treatment group.

During the screening period before study medication was started, the proportion of subjects requiring treatment for a gout flare was similar across treatment groups (7-10%). During the intended 8-week prophylaxis period (day 1 to week 8), a statistically significant greater proportion of subjects in the FBX 120 mg (36%; 97/269) and 240 mg (46%; 61/134) treatment groups required treatment for a gout flare compared to the placebo (20%; 27/134), allopurinol (23%; 61/268) and FBX 80 mg (28%; 73/262) treatment groups. However, after the initial 8-week prophylaxis period, no statistically significant differences in the proportion of subjects requiring treatment for a gout flare were observed between treatment groups during weeks 8 to 28. During the 4-week intervals after the intended 8-week prophylaxis period, the proportion of subjects requiring treatment for a gout flare was initially higher in each treatment group than during the intended 8-week prophylaxis period, but the proportions were generally similar among treatment groups and gradually decreased over time. Between weeks 24 to 28, there were fewer subjects with flares requiring treatment in the active treatment groups (15% for FBX 80 mg and 120 mg, 8% for FBX 240 mg, and 14% for allopurinol) compared to the placebo group (20%). The difference between the FBX 240 mg and placebo treatment groups was statistically significant, but none of the other pair-wise comparisons were statistically significant.

The proportion of subjects requiring treatment for a gout flare was numerically lower during the last 4 weeks of the study (weeks 24 to 28) among the subjects that achieved an average post-baseline serum urate level < 6.0mg/dL compared to the group of subjects that achieved an average post-baseline serum urate level > 6.0 mg/dL (13% versus 18%). Among subjects with no tophus present at baseline, the proportion of subjects requiring treatment for a gout flare was numerically lower over time than for subjects with a tophus at baseline.

7.1.1.2.7. *Quality-of-life results*

Statistically significant improvements from baseline were observed in each of the 8 domains of the SF-36 Health Survey, the Physical Component Summary (PCS) scale, and the Mental Component Summary (MCS) scale for 1 or more treatment groups at week 28 (and/or final visit). At the week 28 visit, each of the treatment groups had statistically significant improvements from baseline in Bodily Pain and the PCS. Subjects in each of the FBX and allopurinol treatment groups had statistically significant improvements from baseline in Role-Physical and Reported Health Transition (which is a general measure of change in the past year). Statistically significant improvements from baseline were also observed for Role-Emotional and

MCS in the FBX 120 mg treatment group and for Physical functioning in the placebo group. Subjects in the FBX 80 mg, FBX 120 mg, and allopurinol treatment groups had statistically significant improvements from baseline in General Health, while subjects in the placebo, FBX 80 mg, FBX 120 mg and allopurinol treatment groups had statistically significant improvements in Vitality. Statistically significant improvements from baseline were also observed in the placebo and FBX 120 mg treatment groups for Mental Health. Statistically significantly greater improvements compared to placebo were observed in the FBX 80 mg and 240 mg treatment groups at the week 28 visit in Role-Physical.

There were statistically significant improvements over time in each of the 5 treatment groups for the MOS Health Distress Scale. The FBX 80 mg group had a statistically significantly greater improvement at the week 28 visit in the MOS Health Distress Scale than the allopurinol arm. Otherwise no treatment related differences were observed for the MOS Health Distress Scale.

All treatment groups showed statistically significant improvements over time (baseline to week 28) in the various gout-specific scales of the GAQ. At week 28, the allopurinol treatment group had statistically significantly greater improvements than the FBX 80 mg and 120 mg cohorts in Productivity, and Gout Flare Symptom Interference. The allopurinol group also had statistically significantly greater improvement than the FBX 80 mg arm in Gout Concern, Well-Being, and Treatment Satisfaction. In addition, the allopurinol treatment group also had statistically significant greater mean values for Treatment Bother (less bothered) and for Treatment Satisfaction (more satisfaction) than the FBX 240 mg arm.

7.1.1.3. *Study C##-010*

7.1.1.3.1. *Study design, objectives, locations and dates*

Study C##-010 was a 52-week, Phase III, randomised, double-blind, parallel-group, active-controlled trial comparing FBX 80 mg and 120 mg/daily to allopurinol 300 mg/day. The objective was to compare the efficacy and safety of FBX to allopurinol in adult subjects with gout.

The study consisted of a wash-out/run-in period that included a screening visit (day -14 for patients who were taking allopurinol or uricosuric drugs prior to the study, or between day -14 and day -3 for subjects not taking such medicines prior to the trial), a day -2 visit, and day 1 visit, followed by a 52 week, double-blind treatment phase. Subjects who completed the 52-week, double-blind phase were given the option of enrolling into a 24 month, open-label extension study with FBX (C##-021). The 14-day wash-out period for allopurinol and uricosuric drugs is sufficient to limit any ongoing efficacy of these medicines on the study endpoints.

In Study C##-010, the first subject was dosed on 11 July, 2002 and the last subject procedure occurred on 20 February, 2004. A total of 112 centres, 106 located in the USA and 6 in Canada, recruited patients. The study was to include European investigating sites but enrolment was complete before any of the European centres could be initiated. There were 3 amendments to the original protocol, all of which were implemented after the commencement of patient recruitment. The amendments contained clarifications about the statistical analysis plan, inclusion and exclusion criterion, and patient assessments. None of the amendments resulted in major changes to the study design, which may have affected the outcome or statistical analysis.

7.1.1.3.2. *Inclusion and exclusion criteria*

To be included in the trial, subjects (male or female) were required to be between 18 to 85 years of age, inclusive. Female subjects were required to be either 2 years post menopausal, surgically sterile or using a stable contraceptive regime for at least 3 months. Patients had to have a history of gout according to the ARA classification. Normal renal function at baseline was a requirement, defined as a serum creatinine level of ≤ 1.5 mg/dL (or 133 μ mol/L) and an estimated creatinine clearance of > 50 mL/min (Cockcroft-Gault formula) on day -14. Subjects needed to have hyperuricaemia, defined as a serum urate > 8.0 mg/dL, on day -2. Exclusion criteria were identical to Study C##-009 (discussed in this report).

7.1.1.3.3. *Study treatments*

Subjects were equally randomized to 1 of 3 treatment groups: FBX 80mg once daily, FBX 120 mg once daily or allopurinol 300 mg once daily. The doses of FBX (80 mg and 120 mg/day) were selected based on the safety and efficacy data from the Phase II, dose response study (TMX-##-004).

Subjects taking allopurinol or uricosuric agents prior to the study discontinued them at the day - 14 screening visit. These subjects began gout prophylaxis medicines at the screening visit (day - 14) consisting of naproxen 250 mg twice daily or colchicine 0.6 mg once daily, and continued taking the medication through to the week 8 visit. Subjects who were not taking uricosuric agents or allopurinol prior to the study did not require a washout period, and did not require naproxen or colchicine prior to day 1. These subjects began prophylaxis (naproxen 250mg twice daily or colchicine 0.6 mg/day) at the day 1 visit and continued them through to week 8. Across the 5 treatment groups, 50-58% used prophylactic colchicine and 42-49% used prophylactic naproxen, for a mean number of 59-61 days. There were no statistically significant differences between the treatment groups with respect to the incidence, type and duration of prophylactic medicine use. Up to 36% of patients required adjustment to their gout prophylaxis (increase or decrease dosage, or a switch to alternative treatment) during the first 8 weeks, and less than 20% discontinued gout prophylaxis before 8 weeks.

If an acute gout attack occurred during the 14-day washout /run-in period, or during the first 8 weeks of the 52-week double-blind treatment period, subjects taking naproxen 250 mg twice daily were allowed to take an additional 250 mg for 1 or 2 days, and subjects taking colchicine 0.6 mg/day were allowed to take an additional 0.6 mg tablet for 1 or 2 days. Subjects who experienced a gout flare on day 1 were not to be randomised until the gout flare resolved.

7.1.1.3.4. *Efficacy variables and outcomes*

The primary efficacy variable was the proportion of subjects whose last 3 serum urate levels were < 6.0 mg/dL. Subjects were evaluated at baseline, weeks 2 and 4, and then every 4 weeks thereafter until week 52.

Secondary efficacy variables were:

- Proportion of subjects whose serum urate levels were < 6.0 mg/dL at each visit,
- Proportion of subjects whose serum urate levels were < 5.0 mg/dL and < 4.0 mg/dL at week 52,
- Mean percentage reduction from baseline to weeks 28 and 52 in serum urate levels,
- Mean percentage reduction in primary tophus size, and the reduction in the total number of tophi in the subset of subjects with a primary palpable tophus at the screening visit,
- Proportion of subjects requiring treatment for a gout flare between weeks 8 and 52, and
- Changes from baseline in QOL instruments such as the SF-36 scale, MOS Health Distress Scale and the GAQ.

7.1.1.3.5. *Randomisation and blinding methods*

Randomization was computer-generated by the statistics department of the study sponsor, and the randomization code was kept in a locked, confidential location.

Beginning at the day 1 visit, subjects and investigators were blinded to all serum urate levels. FBX and allopurinol were over-encapsulated in identical capsules to ensure blinding. Each subject was asked to take 2 capsules, together in the morning, 1 from each supplied de-identified bottle (n = 2).

7.1.1.3.6. *Analysis populations*

The primary and secondary efficacy analyses were based on the ITT population, which included all randomized subjects who received at least 1 dose of study drug and had a serum urate of > 8.0 mg/dL on Day -2 as determined by the central laboratory. Four randomized subjects (1 FBX 80 mg, 1 FBX 120 mg, and 2 allopurinol treated patients) were excluded from the ITT population since their day -2 serum urate level was < 8.0 mg/dL.

7.1.1.3.7. *Sample size*

It was expected that a total of 750 subjects (250 in each treatment group) would be randomized into the trial. The sample size would provide 1) at least 80% power to meet the non-inferiority criteria between at least 1 FBX treatment group and the allopurinol arm for the primary efficacy variable, and 2) at least 90% power to detect a 15% difference between a FBX treatment group and allopurinol for the primary efficacy outcome. For the determination of the non-inferiority margin, it was assumed a response rate of 60% could be expected for allopurinol and at least 64% for the FBX dose groups. These assumptions were based on the data from Study TMX-##-004 and published historical data for allopurinol.

7.1.1.3.8. *Statistical methods*

The comparisons for the primary efficacy variable (proportion of patients with last 3 urate levels < 6.0 mg/dL) were done sequentially using a closed testing procedure within each of 2 steps. The first step involved comparing each FBX treatment group to allopurinol to test for non-inferiority. If each dose of FBX was shown to be non-inferior to allopurinol, the analysis proceeded to step 2. In the second step, the FBX 80 mg and 120 mg treatment groups were compared to allopurinol for superiority. The overall 0.05 alpha level was maintained by using binomial 97.5% CIs for the non-inferiority tests, and Hochberg's method for the superiority testing. Pair-wise comparisons between treatment groups were made with Fisher's exact test. Superiority of a FBX treatment group to placebo was declared if the p-value from the CMH test was less than or equal to the critical significance level based on Hochberg's method. Non-inferiority to allopurinol was declared if the absolute value of the lower bound of the 97.5% CI did not exceed 10%. A sensitivity analysis was conducted for the primary efficacy outcome by using the available (1 or 2) serum urate levels to determine response for subjects who prematurely discontinued (these subjects were assigned non-responder status in the primary analysis). The effect of various patient factors (age, gender, ethnicity, baseline BMI, alcohol use, compliance, baseline serum creatinine, use of previous urate lowering therapy, baseline serum urate levels, and presence of baseline palpable tophus) on the primary outcome measure was also assessed.

For the secondary efficacy measures, pair-wise comparisons between all treatment groups were made using Fisher's exact test for the proportion of patients whose serum urate levels were < 6.0 mg/dL and the proportion of subjects requiring treatment for a gout flare; ANOVA was used for the percentage reduction in serum urate levels and QOL tools; and the Wilcoxon rank-sum test was employed for the percentage reduction in primary tophus size and the reduction in the total number of tophi. No adjustments were made to the overall 0.05 alpha level for the secondary efficacy variables.

7.1.1.3.9. *Participant flow*

A total of 760 subjects were randomized into the trial and received at least 1 dose of study medication: 256 received FBX 80 mg/day, 251 received FBX 120 mg/day, and 253 received allopurinol 300 mg/day. Overall, 33.2% (252/760) of subjects prematurely discontinued treatment. A lower proportion of patients in the allopurinol treatment group prematurely discontinued therapy (26.1%; 66/253) compared to the FBX treatment groups (34.4% [88/256] from the FBX 80 mg group, and 39.0% [98/251] from the FBX 120 mg arm). Of the subjects who prematurely discontinued, 44.0% (111/252) discontinued within the first 12 weeks and discontinuation rates declined after thereafter. A greater proportion of subjects in the FBX 120

mg treatment group prematurely discontinued within the first 12 weeks of the study (53.1%; 52/98) compared to the FBX 80 mg (40.1%; 36/88) and allopurinol 300 mg (34.9%; 23/66) treatment groups. The most frequent primary reason for discontinuing study drug overall was lost to follow-up (25%, 64 subjects). However, a greater proportion of subjects in the FBX 120 mg group prematurely discontinued treatment due to gout flare and adverse events (28.6% [28/98] and 23.5% [23/98], respectively) compared to the FBX 80 mg arm (11.4% [10/88] and 18.2% [16/88], respectively) and allopurinol 300 mg (13.6% [9/66] and 12.1% [8/66], respectively) treatment groups.

7.1.1.3.10. *Major protocol violations/ deviations*

A total of 50 subjects (16 in the FBX 80 mg group, 15 in the FBX 120 mg arm, and 19 in the allopurinol group) had deviations from the admission criteria. Four subjects (2 in the FBX 80 mg group, 1 in the FBX 120 mg arm, and 1 in the allopurinol group) were prematurely discontinued due to admission criteria violations. Most of the admission criteria violations were associated with subjects whose alcohol intake was > 14 drinks/week (7 FBX 80 mg, 4 FBX 120 mg, and 5 allopurinol treated subjects). Eleven subjects had abnormal renal function at baseline (4 FBX 80 mg, 3 FBX 120 mg, and 4 allopurinol treated patients) but for 10 of the 11 subjects their estimated or measured creatinine clearance was > 50mL/min, and so they were allowed to enter the study. Other significant protocol deviations at entry were 4 subjects with a day -2 serum urate level < 8.0 mg/dL (1 in the FBX 80 mg group, 1 in the FBX 120 mg arm, and 2 subjects in the allopurinol cohort), 5 subjects had concomitant thiazide diuretic therapy (2 FBX 80 mg and 3 FBX 120 mg treated subjects), 3 subjects had active liver disease (2 FBX 80 mg patients, and 1 allopurinol subject), 3 subjects (all in the allopurinol group) reported a history of cancer, and 2 subjects had concomitant urate-lowering therapy with allopurinol (1 FBX 120 mg treated patient and 1 allopurinol subject).

During the study, 8 subjects (1 FBX 80 mg, 4 FBX 120 mg and 3 allopurinol patients) received incorrect treatment at some point during the study. Regarding prohibited concomitant medication use during the trial, a noteworthy proportion of subjects in all treatment groups received prednisone > 10 mg/day: 19% for FBX 80 mg, 25% for FBX 120 mg, and 15% for the allopurinol group.

7.1.1.3.11. *Baseline data*

There were no clinically relevant differences across the 3 treatment groups in terms of demographic or baseline disease characteristics. The mean age of patients was 51.8 years (range: 23 to 83 years). The majority of subjects were Caucasian (77.2%; 587/760) and most subjects were male (95.9%; 729/760). The majority of subjects reported the use of alcohol (66.1%; 502/760) and were non-/ex-tobacco users (82.8%; 629/760). The mean BMI for all subjects was 32.5 kg/m², and 62% had a BMI of > 30 kg/m². Just less than half (43.6%; 331/760) of subjects had a history of hypertension and one third had a history of hyperlipidaemia (33.6%; 255/760). Ten subjects (1.3%) had a history of congestive heart failure, 9.7% (74/760) had a history of cardiovascular disease, and 7.0% (53/760) had diabetes. Across the 3 treatment groups, 14% to 20% of patients used low dose aspirin. The mean calculated creatinine clearance at baseline (using ideal body weight) was 90.0 mL/min.

There were no statistically significant differences between the 3 treatment groups in any gout history feature. The mean number of years with gout ranged from 11.5 to 12.6 years across the treatment groups. The majority of subjects in each treatment group experienced their last gout flare within 1 year of enrolment (87.4%; 664/760). A history of renal calculi was present in 16.2% of subjects (123/760). A total of 19.9% (151/760) of subjects had a primary palpable tophus, with an average of 7 years since onset of first tophus. The most common locations for the tophi were elbow, ankle/foot (including the toe and instep), and wrist/hands.

There was no statistically significant difference among the treatment groups in baseline serum urate level. Overall, the mean serum urate levels at baseline ranged from 9.8 to 9.9 mg/dL and

41.4% of all subjects (313/756) had a baseline serum urate level > 10 mg/dL. Across all treatment groups, the most frequently occurring baseline serum urate level was between 9.0 and < 10.0 mg/dL (31.2%; 236/756).

7.1.1.3.12. *Results for the primary efficacy outcome*

The proportion of subjects in Study C##-010 whose last 3 serum urate levels were < 6.0 mg/dL were 53.3% (136/255) in the FBX 80 mg group, 61.6% (154/250) in the FBX 120 mg arm and 21.1% (53/251) in the allopurinol group. The 97.5% CIs for the differences in response rates for FBX 80 mg versus allopurinol were 23.1% and 41.3%; and for FBX 120 mg versus allopurinol were 31.5% and 49.5%. This result demonstrated the non-inferiority of each FBX dose relative to the allopurinol 300 mg/day. Additionally, the differences between each of the FBX treatment groups (32% difference for FBX 80 mg and 41% difference in proportions for 120 mg) and allopurinol confirmed that each FBX dose was statistically superior to allopurinol ($p < 0.001$ for both comparisons). The difference in response between the FBX 80 mg and 120 mg treatment groups was not statistically significant.

Response rates were also compared using CMH methodology adjusting for gender, age, race, overall compliance, baseline renal function, baseline serum urate level, baseline palpable tophus present, previous use of urate lowering therapy, history of renal calculi, history of cardiovascular risk factors, alcohol use, baseline BMI, and use of low-dose aspirin. After adjusting for each factor, statistically significant pair-wise differences in favour of FBX were observed between each of the FBX dose groups and allopurinol for the primary outcome measure. However, some subgroups were too small to draw meaningful conclusions (for example only 11 subjects in total had impaired renal function at baseline).

A sensitivity analysis was conducted for the primary efficacy outcome using the available (1 or 2) serum urate levels to determine response for subjects who prematurely discontinued before at least 3 serum urate levels were obtained. In the primary analysis these subjects were assigned non-responder status. In all of the treatment groups the proportions of subjects whose last 3 serum urate levels were < 6.0 mg/dL were slightly higher in this sensitivity analysis compared to the overall analysis. Among ITT subjects, response rates were 59% in FBX 80 mg arm, 71% in the FBX 120 mg group, and 24% in the allopurinol treatment group. The differences between each of the FBX treatment groups and allopurinol were statistically significant ($p < 0.001$). In addition, the response rate in the FBX 120 mg group was statistically superior to the FBX 80 mg arm ($p < 0.01$).

Response rates (that is last 3 serum urate levels < 6.0 mg/dL) stratified by baseline serum urate levels were lower in the allopurinol arm compared to each of the FBX treatment groups. This was particularly evident in the subgroup of patients with a baseline serum urate level of at least 10.0 mg/dL.

7.1.1.3.13. *Results for other efficacy outcomes*

7.1.1.3.13.1. Proportion of subjects whose serum urate levels were < 6.0 mg/dL at each visit

The proportions of subjects whose serum urate were < 6.0 mg/dL were statistically significantly greater in each of the FBX treatment groups compared to the allopurinol at weeks 28 and 52, as well as at their final visits. In addition, at week 28, a statistically greater proportion of subjects in the FBX 120 mg group (81.8%; 130/159) compared to the FBX 80 mg arm (71.5%; 133/186) had a serum urate level < 6.0 mg/dL. Throughout the course of the 52-week study, response rates for the proportions of subjects achieving a serum urate level of < 6.0 mg/dL ranged from 69% to 82% in the FBX 80 mg group, 79% to 88% in the FBX 120 mg arm and 36% to 45% in the allopurinol treatment group.

7.1.1.3.13.2. Proportion of subjects whose serum urate levels were < 5.0 mg/dL and < 4.0 mg/dL

The proportions of subjects whose serum urate levels were < 5.0 mg/dL were statistically higher in each of the FBX treatment groups compared to allopurinol therapy at the week 28,

week 52, and final visits. Furthermore, a statistically greater proportion of subjects in the FBX 120 mg group compared to the FBX 80 mg arm had serum urate levels < 5.0 mg/dL at the week 28, week 52, and final visits.

Similarly, the proportions of subjects whose serum urate levels were < 4.0mg/dL were statistically greater in each of the FBX groups compared to the allopurinol arm at the week 28, week 52, and final visits. Moreover, a statistically higher proportion of subjects in the FBX 120 mg group compared to the FBX 80 mg group had serum urate levels < 4.0 mg/dL at the week 28, week 52, and final visits.

7.1.1.3.13.3. Mean percentage reduction in serum urate levels

The mean percentage changes from baseline in serum urate levels were statistically higher in each of the FBX treatment groups compared to the allopurinol treated subjects. In addition, at weeks 28 and 52, as well as the final recorded visit, a statistically greater mean change in serum urate levels was observed in the patients who received FBX 120 mg/day versus those who took FBX 80 mg/day.

7.1.1.3.13.4. Percentage reduction in primary tophus size

A total of 150 subjects (19.7% of 760) had a primary tophus at baseline: 52 in the FBX 80 mg arm, 53 in the FBX 120 mg group, and 45 subjects in the allopurinol group. Among subjects with a primary tophus at baseline, there were no statistically significant differences between any of the 3 treatment groups for the percentage changes from baseline in primary tophus size at the week 52 (or final visit). At week 28, the FBX 120 mg treatment group showed a statistically significant median percentage reduction in primary tophus size compared to both allopurinol and FBX 80 mg. The median percentage reduction from baseline to week 28 was 29.5% in the FBX 80 mg arm (n = 36), 49.5% in the FBX 120 mg group (n = 28), and 28.6% in the allopurinol treatment group (n = 33).

Like Study C##-009, an additional analysis of the percentage reduction in primary tophus size excluding elbow locations was performed. Among subjects with a primary palpable tophus at baseline, the percentage change in primary tophus size (excluding elbow locations) was not statistically different between any of the treatment groups at week 28. However at week 52, the FNX 80 mg group (87.0% reduction; n = 17) had a statistically greater median percentage reduction in tophus size compared to allopurinol (28.7% reduction; n = 14). The FBX 120 mg group showed a median 72.5% reduction in tophus size at week 52 but this was not statistically significant for either pair-wise treatment comparison.

Among subjects with a primary palpable tophus at baseline, the median percentage change from baseline in primary tophus size was numerically greater in the group that achieved an average post-baseline serum urate level < 6.0 mg/dL (n = 89) compared to those who didn't achieve that target serum urate level (n = 55). At week 52, the median percentage reduction from baseline in the primary tophus size was 75.0% in the group of subjects that achieved an average post-baseline serum urate level < 6.0 mg/dL compared to 49.7% in the group of subjects that achieved an average post-baseline serum urate level > 6.0 mg/dL. Among the 207 subjects with a primary palpable tophus at baseline and at least 1 post-baseline serum urate level, the number of subjects with an average post-baseline serum urate level < 6.0 mg/dL was greater in the FBX treatment groups (42 subjects in the 120 mg dose group, and 36 in the 80 mg dose arm) versus 11 subjects in the allopurinol treatment group.

7.1.1.3.13.5. Reduction in total number of tophi

There were no statistically significant differences between treatment groups in the change from baseline in number of tophi at the week 28, week 52 or final visit. In each treatment group, there was little change in median values over time. A decrease in the mean number of tophi was noted in each treatment group and the mean change from baseline to week 52 was -0.4 tophi in the FBX 80 mg arm, -1.0 in the FBX 120 mg cohort, and -0.7 tophi in the allopurinol treatment group.

7.1.1.3.13.6. Proportion of subjects requiring treatment for gout flare

The majority of subjects in all treatment groups received treatment for a gout flare during the study with similar percentages of affected patients in each treatment group: 63.9% (163/255) for the FBX 80 mg arm, 71.6% (179/250) for the FBX 120 mg group, and 64.9% (163/251) for the allopurinol treatment group. The gout flare incidence was similar in the screening phase of the study (affecting 8-11% of patients in each treatment group), but during the 8-week prophylaxis phase (day 1 to week 8), a statistically higher proportion of patients in the FBX 120 mg group (36.0%; 90/250) required treatment for a gout flare compared to both FBX 80 mg (21.6%; 55/255) and allopurinol (20.7%; 52/251). However, no statistically significant difference was observed between treatment groups after the intended 8-week prophylaxis (that is weeks 8-52) or for the overall 52-week study period.

7.1.1.3.13.7. Quality-of-life results

Statistically significant improvements from baseline were observed in each of the 8 domains of the SF-36 Health Survey, the Physical Component Summary (PCS) scale, and the Reported Health Transition index for 1 or more treatment groups at week 52 (and/or final visit). At the week 52 visit, each of the treatment groups had statistically significant improvements from baseline in Role-Physical, Bodily Pain, Vitality, PCS, and Reported Health Transition. Subjects in the FBX 80 mg and allopurinol treatment groups had statistically significant improvements from baseline in Physical Functioning, General Health and Social Health Functioning. In addition, subjects in the allopurinol group had statistically significant improvements from baseline in Role-Emotional and the MCS.

There were statistically significant improvements over time in each of the treatment groups for the MOS Health Distress Scale, but no treatment related differences were observed at any time point in the study (weeks 24 or 52, as well as final visit).

All treatment groups showed statistically significant improvements over time (baseline to week 24 and 52, as well as the final visit) in the various gout-specific scales of the GAQ. At week 52, the allopurinol treatment group had statistically significantly greater improvements than the FBX 120 mg arm in Gout Concern, Gout Pain and Treatment Satisfaction.

7.1.2. Other efficacy studies

7.1.2.1. *Studies TMX-##-004 and TMX-##-005*

7.1.2.1.1. *Design and objectives*

Study TMX-##-004 was a Phase II dose-response study with the primary objective of identifying doses of FBX that could be investigated in the pivotal Phase III clinical trials. It was a randomised, double-blind, parallel-group, placebo-controlled trial conducted at 24 sites in the USA between 31 January 2001 and 9 July 2001. The study had a 2-week run-in period followed by a 4-week treatment phase. There were 2 amendments to the original protocol, the first of which was implemented immediately prior the commencement of patient recruitment. The amendments contained clarifications about the statistical analysis plan, inclusion and exclusion criterion, and patient assessments. Neither of the amendments resulted in major changes to the study design, which may have affected the outcome or statistical analysis.

Patients who were taking allopurinol or uricosuric drugs prior to the study discontinued these treatments at the screening visit on day -14. Subjects who were not taking prior allopurinol or uricosuric drugs started a 2-week run-in phase prior to randomization in order to begin prophylactic treatment with colchicine. All patients began colchicine 0.6 mg twice daily at the day -14 screening visit and continued this therapy for 4 weeks in total, ceasing the day before the scheduled day 14 study visit (that is day 13). The prophylactic dose of colchicine could be reduced to 0.6 mg daily if the subject was experiencing an AE to that therapy. Subjects had a baseline visit on day -2 prior to randomization on day 1. A 24-hour urine uric acid collection was done on day -1 through to day 1 to classify patients as under-excretors (≤ 800 mg/day) or

over-producers (> 800 mg/24 hours) of uric acid. Double-blind treatment visits occurred on days 7, 14, 21 and 28.

Study TMX-##-005 was the long-term, open-label extension (OLE) phase of Study TMX-##-004. It continued patient care for up to 5 years in those who had completed the controlled study without experiencing any serious study drug related AEs. The submission contained an interim analysis of efficacy data obtained between 21 March 2001 and 15 September 2003. The data recorded at the day 28 visit in Study TMX-##-004 was used as the day 1 information for the OLE trial. Study visits were scheduled for weeks 2 and 4, and every 4-8 weeks thereafter.

7.1.2.1.2. *Inclusion and exclusion criteria*

The study enrolled patients between the ages of 18 and 85 years with hyperuricaemia (defined as serum urate ≥ 8.0 mg/dL) with a history or presence of gout according to the ACR criteria. Patients were required to have a serum creatinine of ≤ 1.5 mg/dL and a creatinine clearance of ≥ 50 mL/min by Cockcroft-Gault estimation. Subjects were excluded if they had any change in thiazide diuretic therapy or CS (< 10 mg/day of prednisolone or equivalent) within the preceding month, history of excessive alcohol intake (≥ 14 drinks/week), BMI > 50 kg/m 2 , hepatic dysfunction (serum transaminases > 1.5 ULN) or any other significant medical condition considered by the investigator that would interfere with the treatment safety (for example a clinically significant ECG abnormality).

7.1.2.1.3. *Study treatment, blinding and randomization*

Qualifying subjects were randomized by a computer generated program into 1 of 4 treatment groups: placebo, FBX 40 mg once daily (given as 2 x 20 mg tablets), FBX 80 mg once daily (given as 4 x 20 mg tablets) or FBX 120 mg once daily (given as 6 x 20 mg tablets). The Teijin formulation of FBX tablets was used in this trial. All patients received a total of 6 tablets daily, to be taken together in the morning. A variable quantity of matching placebo tablets (in each treatment assignment) made up the total amount of daily tablets ($n = 6$) to be taken. The doses of FBX investigated in Study TMX-##-004 were identified from the safety and PK data in the Phase I Study TMX-##-001 in which single and repeat (14 day) oral doses of FBX up to 240 mg were well tolerated in healthy male and female volunteers. The doses of FBX used in that trial resulted in 40-70% decreases from baseline in serum urate levels.

In the OLE study, all subjects initially received FBX 80 mg/day and titration (up to 3 times, to doses of 40 mg, 80 mg or 120 mg per day) were allowed between weeks 4 and 24 upon review of the patient's serum urate level and AEs. Subjects were to be stabilized on a dose of FBX by the week 28 visit, and were to remain on that dose thereafter. In the OLE phase, colchicine 0.6 mg twice daily was re-initiated on day 1 and prescribed until the day before the week 4 visit. After the week 4 assessments, ongoing colchicine prophylaxis was at the discretion of the investigator.

7.1.2.1.4. *Efficacy measures*

The primary efficacy variable in Study TMX-##-004 was the proportion of subjects in each treatment group whose serum urate level decreased to < 6.0 mg/dL at day 28. In addition, the responder rates were summarized by subgroups of interest at baseline: serum urate level (≤ 9.0 mg/dL, 9.1-10 mg/dL and > 10.0 mg/dL), gender, renal function (CrCL 50-80 mL/min or > 80 mL/min), baseline uric acid production (over-producer versus under-excretor) and tophus present (yes/no) at entry. Serum urate was measured by a central laboratory using 2 different methods (enzymatic and HPLC) in this study. During the trial, there was a high correlation ($r = 0.97$) between serum urate levels determined by the enzymatic and HPLC methods.

Secondary efficacy endpoints in Study TMX-##-004 included:

- Proportion of subjects whose serum urate decreased to < 5.0 mg/dL and < 4.0 mg/dL by day 28,
- Proportion of subjects whose serum urate decreased to < 6.0 mg/dL at each visit,

- Mean percentage reduction from baseline in serum urate level,
- Mean percentage reduction from baseline in 24-hour urinary uric acid excretion,
- Incidence of gout flares during the study,
- Changes in Plain X-ray abnormalities between baseline and day 28 (central reader), and
- QOL assessments (using the SF-36 scale) between baseline and day 28.

The primary efficacy outcome in the OLE study was the proportion of subjects whose serum urate levels decreased to or was maintained at < 6.0 mg/dL. The secondary efficacy endpoints in Study TMX-##-005 were the mean percentage reduction from baseline in serum urate levels using the enzymatic method, percentage of subjects whose last 3 serum urate levels were < 6.0 mg/dL, percentage of subjects whose serum urate levels were < 5.0 and < 4.0 mg/dL, the incidence of gout flare, QOL measures and the percentage change in tophus size based on MRI measurements.

7.1.2.1.5. *Sample size and statistical methods*

The primary and secondary efficacy analyses in Study TMX-##-004 were performed on the ITT population, which included all randomized subjects who had a serum urate level of at least 8.0 mg/dL on day -2. For the primary efficacy outcome, the rates of response in each of the 4 treatment groups were summarized and compared between each of the FBX treatment groups and placebo using Fisher's exact test. Statistical significance was determined using Hochberg's method for multiple comparisons at the 0.049 level. For both the primary and secondary efficacy endpoints, analyses were performed using the LOCF method to impute missing data.

For Study TMX-##-004 it was estimated that 23 subjects per treatment group would provide at least 90% power to detect a difference in the primary outcome measure between FBX and placebo with a 2-sided significance level of 0.05. This assumes an 80% responder rate for any of the FBX dose groups and 30% for placebo. If the trial had a dropout rate of 20%, it was estimated that 120 subjects (30 per treatment group) would need to be enrolled.

7.1.2.1.6. *Subject disposition and protocol deviations*

A total of 153 patients were randomized into the Phase II trial and received at least 1 dose of study medication: 38 received placebo, 37 received FBX 40 mg, 40 received FBX 80 mg and 38 received FBX 120 mg. Overall, 8 patients prematurely discontinued from the study: 2 in the placebo group (1 because of an AE and the other because of gout flare), 1 FBX 40 mg patient (due to AE), 3 FBX 80 mg subjects (2 due to AEs, and 1 due to non-compliance with drug dosing), and 2 FBX 120 mg/day treated patients (both due to AEs). However, 13 subjects were excluded from the ITT population as their day -2 serum urate was collected outside the visit window period.

A total of 15 patients (1 placebo, 3 FBX 40 mg, 6 FBX 80 mg, and 5 FBX 120 mg) had deviations in the admission criteria for Study TMX-##-004, most of which were due to subjects having impaired renal function (to < 50 mL/min) at baseline. None of the protocol deviations on study had the ability to compromise the data analysis apart from 1 patient in the placebo who appeared to have been incorrectly dispensed FBX therapy from day 1.

A total of 116 subjects entered into the OLE phase (Study TMX-##-005) and 61 (52.6%) remained in the study at the time of interim data analysis. Most patients (62.9%; 73/116) did not undergo a dose adjustment, but single upward dose adjustments occurred in 24% of subjects. The number of subjects on a stable dose of FBX 80 mg/day was 77 (66.4%), FBX 40 mg/day was 9 (7.8%) and FBX 120 mg/day was 30 (25.9%).

7.1.2.1.7. *Baseline data*

No relevant differences were observed between the treatment groups for demographic characteristics. The mean age of subjects ranged from 52.2 to 56.2 years across the 4 treatment groups. The study population was predominately Caucasian (86.9%; 133/153) and male (88.9%; 136/153). The mean BMI ranged from 31.6 to 33.2 kg/m² across the treatment groups.

The mean baseline serum urate levels were slightly higher in all treatment groups using the enzymatic method (9.24 to 9.92 mg/dL among the treatment groups) compared to the HPLC method (8.32 to 9.04 mg/dL). The majority (78.7%; 118/150) of patients were categorized as under-excretors of uric acid (<800 mg/day) at baseline, and 23.5% (36/153) of subjects had a palpable tophus at screening. Among those who had baseline joint x-rays, the majority of FBX treated subjects had abnormalities (61%; 61/100) compared to placebo patients where less than half had abnormalities (47.2%; 17/36).

Almost half of all randomized subjects had a history of hypertension (49.0%; 75/153) or hyperlipidaemia (46.4%; 71/153). Existing cardiovascular disease was documented in 22.9% (35/153) and 13.1% (20/153) had diabetes.

7.1.2.1.8. *Efficacy results*

At day 28, a statistically higher proportion of subjects in each of the FBX treatment groups had a serum urate level of < 6.0 mg/dL compared to the placebo group (as measured by either serum urate evaluation method). Within the FBX treatment groups, the proportion of subjects reaching the target serum urate concentration was higher with increasing dose.

When the primary efficacy endpoint was analysed by subgroup of interest at baseline, the same pattern of response in favour of FBX versus placebo, and increasing dose of FBX was observed. However, some of the subgroups had insufficient patient numbers to draw meaningful conclusions (for example there were only 1-6 females in each of the 4 treatment groups).

Similar to the primary efficacy result, at the completion of treatment a statistically greater proportion of patients in each of the FBX dose groups (enzymatic method: 21-88%; HPLC method: 35-94%) achieved a serum urate of < 5.0 mg/dL compared to placebo (zero patients). Using a serum urate level of < 4.0 mg/dL at day 28, a statistically higher proportion of patients in the FBX 80 mg group (enzymatic method: 19%; HPLC method: 22%) and FBX 120 mg therapy (enzymatic method: 56%; HPLC method: 71%) achieved a response compared to placebo (zero subjects). Within the FBX dose group comparisons, success rates defined by levels of serum urate (< 5.0 mg/dL and also < 4.0 mg/dL) were statistically higher with increasing FBX dose.

A statistically higher percentage of patients in each of the FBX treatment groups compared to placebo had a serum urate level of < 6.0 mg/dL at each visit (days 7, 14 and 21) as determined by either serum urate evaluation method.

At day 28, the mean percentage reduction in serum urate level (enzymatic method) was 2.15% for placebo, 36.6% for FBX 40 mg, 44.3% for FBX 80 mg and 59.1% for FBX 120 mg. Each FBX treatment group showed a statistically greater percentage reduction from baseline in serum urate compared to placebo, and furthermore, the response was greater with increasing FBX dose. The results using the HPLC method of serum urate estimation showed the same pattern of response. In addition, the day 28 results were largely evident by the day 7 visit assessment in all treatment groups.

The mean percentage reduction from baseline to day 28 in urine uric acid levels was statistically greater in each of the FBX treatment groups (43.6%-46.5% among the FBX groups) compared to placebo (5.9% reduction from baseline).

Among the ITT population, the incidence of gout flares during the 28-day study was similar between the placebo (37.1%; 13/35), FBX 40 mg/day (35.3%; 12/34) and FBX 80 mg/day (40.5%; 15/37) treatment groups. However, a greater proportion of patients treated with the

highest dose (120 mg/day) of FBX developed gout flares (55.6%; 19/34). The most frequent anatomical location for an acute gout attack was the toe, which was reported by 20-26% of subjects in each treatment group. During the 2-week interval when colchicine and FBX were co-administered, the incidence of gout flares was considerably lower in all treatment groups (8%-15%) than the 2-week period when FBX was taken alone (29%-41% across the 3 FBX treatment groups). Patients with palpable tophi at baseline had a similar incidence of gout flares to those without tophi at entry.

The majority of bone and soft tissue abnormalities that were identified on plain x-rays at baseline remained the same at day 28 in each of the 4 treatment groups. This reflects an insufficient period of follow-up for this endpoint. Similarly, no specific treatment related trend was apparent for mean changes from baseline to day 28 in QOL variables.

In Study TMX-##-005, the ability of FBX to effectively lower and maintain a serum urate level of < 6.0 mg/dL was demonstrated in 79% (63/80) of subjects at 1 year, 77% (54/70) of patients at 2 years, 84% (54/64) of subjects at 3 years and 90% (52/58) of subjects at 4 years. The majority of subjects who continued long-term FBX treatment were taking 80 mg/day. After the first year of FBX treatment in Study TMX-##-005, less than 10% of all subjects received treatment for a gout flare. The overall incidence of gout flares gradually declined over 5 years with continued FBX treatment, with the greatest reduction noted in the patient group receiving 80 mg/day. After 1 year of FBX therapy, subjects had on average less than 1 gout flare per year, which continued to decline over time (up to 5 years of follow-up).

Tophi were not specifically measured in Study TMX-##-005, but their presence or absence on physical examination was noted at baseline and on sequential study visits. Only 26 patients entered the OLE phase with a palpable tophus. Regarding tophi resolution, 77% (20/26) of subjects had this recorded at 1 or more examinations in Study TMX-##-005.

7.1.2.2. *Study C##-021*

Study C##-021 was a 24-month OLE trial for subjects who had completed either Study C##-009 or Study C##-010. Of the 1280 subjects who completed the 2 pivotal studies (C##-009 and C02-010), 1086 subjects (84.8%) enrolled in the OLE Study C##-021 and this constituted the cohort for the efficacy analysis. The data cut-off date for the report was 16 November 2005. The original study design was for a single-arm study in which all subjects received FBX 80 mg/day, with the option to up-titrate the dose to 120 mg/day. However, following a request from the FDA to include an active comparator in this study, protocol amendment 2 added an allopurinol treatment group. Subjects enrolled after the implementation of protocol amendment 2 were randomized 2:2:1 to receive FBX 80 mg/day, FBX 120 mg/day or allopurinol 300 mg/day (normal renal function) or 100 mg/day (if serum creatinine was between 1.5 and 2.0 mg/dL). The number of subjects initially assigned to FBX 80 mg/day was 649, FBX 120 mg/day was 292, and allopurinol was 145. Some subjects had a change of study medication or a dose change in Study C##-021, and therefore the total number of subjects exposed to at least 1 study medication in Study C##-021 was higher than the enrolment numbers: 801 for FBX 80 mg, 487 for FBX 120 mg, and 178 for allopurinol therapy. As per the study protocol, subjects were allowed to switch treatment or titrate up the FBX dose if the serum urate level was > 6.0 mg/dL during the first 6 months of treatment. In addition, a subject was to be discontinued due to therapeutic failure (defined as serum urate > 6.0 mg/dL at 6 months). Of the 941 subjects initially assigned to 1 of the FBX doses, 33 subjects (3.5%) switched to allopurinol. In particular, less than 1% of subjects (2/649) on FBX 80 mg, and 8.5% of subjects (24/292) on FBX 120 mg switched to allopurinol. The primary reason for treatment switch was therapeutic failure (serum urate level > 6.0 mg/dL). For subjects initially randomized to allopurinol, 59.3% (86/145) switched to FBX. Prophylactic medication (colchicine or naproxen) for gout flares was prescribed during the first 8 weeks of treatment in this study.

Final visit assessments performed in the Phase III pivotal studies were considered to be the day 1 (visit 1) assessments for this OLE study. Efficacy assessments included serum urate levels (collected at month 1 and 2, and bimonthly thereafter), proportion of subjects requiring treatment for gout flares, and the percentage of patients with a reduction (complete and 50%) in primary tophus size.

Patients were considered to be on stable treatment after the period when switches of drug or dose were no longer allowed. The duration of stable treatment was defined by determining the first day of a subject's final treatment until the last day of treatment. For the time interval of < 1 year, the exposure (in Patient-Years [PY]) was 560.0 for FBX 80 mg, 340.5 for FBX 120 mg, and 71.0 for allopurinol.

7.1.2.2.1. *Serum urate levels*

Both FBX 80 mg and 120 mg once daily were effective in reducing and maintaining the serum urate level to < 6.0 mg/dL. By the end of 6 months of treatment, the percentages of subjects whose serum urate levels were < 6.0 mg/dL on their initial treatment assignment were 86.2% (399/463) for FBX 80 mg, 89.8% (177/197) for FBX 120 mg, and 71.4% (45/63) in the allopurinol treatment groups.

However, these percentages, especially those of allopurinol, are influenced by the option subjects had to switch treatment or FBX dose. Subjects whose serum urate levels remained > 6.0 mg/dL while receiving allopurinol either discontinued from the study or switched treatment to FBX, therefore, the percentages of subjects whose serum urate levels were < 6.0 mg/dL would be expected to increase over time. In order to assess the effect of FBX and allopurinol on serum urate levels prior to drug or dose switch, an analysis of the final visit prior to drug or dose switch was performed. The percentages of subjects on initial treatment assignment whose serum urate levels were < 6.0 mg/dL at the time of the final visit were 71.4% (455/637) for FBX 80 mg, 80.2% (227/283) for FBX 120 mg and 31.9% (45/141) in the allopurinol treatment group.

Approximately 2/3 of the patients (67.1%; 55/82) that switched from allopurinol (in the previous Phase III studies) to FBX (either dose) achieved the target serum urate concentration of < 6.0 mg/dL, and a small percentage of subjects (9.1%; 2/22) responded to allopurinol after failing treatment with FBX. Many subjects (87%) who responded to FBX 120 mg/day in the Phase III studies maintained the target serum urate concentration response when reduced in dose to FBX 80 mg/day in Study C##-021.

7.1.2.2.2. *Gout flare results*

Treatment switches may induce fluctuation in serum urate levels resulting in mobilization of urate crystals and increasing gout flares. In order to minimize the effect of this when evaluating the results, the percentage of subjects requiring treatment for a gout flare was summarised by subjects prior to any switches in drug or dose. At 6 months, the percentage of patients on their initial treatment assignment requiring treatment for a gout flare was 10.6% (54/509) for FBX 80 mg, 19.6% (43/219) for FBX 120 mg and 9.3% (7/75) for allopurinol. A reduction in gout flare rate to < 10% beyond 6 months of treatment (and < 5% after 16 months) was noted in all 3 treatment groups. This is not unexpected finding as only subjects who maintained a serum urate level of < 6.0 mg/dL continued treatment, as per the study protocol. It was estimated that the baseline gout flare rate was 20%, the rate observed in the placebo group of the Phase III study C##-009 during a 2-month period after the prophylaxis. The results of the OLE Study C##-021 indicate that a sustained reduction in serum urate level to < 6.0 mg/dL is associated with a significant reduction in the frequency of gout flares in the long-term.

7.1.2.2.2.1. *Tophi*

At baseline, tophi were present in 19.7% (214/1086) of subjects. At the final visit prior to any switches in drug or dose, the percentage of subjects on their initial treatment assignment with

complete resolution of tophi were 38% for FBX 80 mg, 36% for FBX 120 mg, and 17% for allopurinol. The proportions of subjects with at least a 50% reduction in primary tophus size were 65% for FBX 80 mg, 71% for FBX 120 mg, and 57% for the allopurinol treatment group.

7.1.2.3. Study F-GT##-153

7.1.2.3.1. Design and objectives

Study F-GT##-153 was a Phase III, randomized, double-blind, active-controlled study with the primary objective of comparing the efficacy and safety of FBX 40 mg/day and 80 mg/day to allopurinol in subjects with hyperuricaemia and gout. In 2004, the FDA requested the sponsor perform this trial as the lower dose of FBX 40 mg/day had not been investigated in a Phase III study. In addition, the study also had a safety outcome of special interest to examine. In the preceding Phase III studies involving FBX 80-240 mg/day, there was a small but comparatively higher incidence of adverse cardiovascular events (not statistically significant) in the FBX treatment groups compared to allopurinol therapy, for which the FDA requested further characterization of the risk-benefit of FBX, particularly at the most commonly used commercial dose of 80 mg once daily. Patients with gout have a high background incidence of risk factors for atherosclerotic cardiovascular disease due to co-morbidities and demographic features of the target population. The study was conducted at 324 sites in the USA between 16 February 2007 and 12 March 2008. The study had a run-in period of up to 30 days followed by a 6-month active treatment phase. In addition to newly identified subjects, patients who had completed either of the 2 OLE studies (TMX-##-005 or C##-021) were eligible to enter into this trial.

There were 2 amendments to the original protocol, both of which were implemented after the commencement of patient recruitment. The amendments contained clarifications about the statistical analysis plan, inclusion and exclusion criterion (in particular, defining the levels of renal impairment), concomitant medication use and patient assessments. Neither of the amendments resulted in major changes to the study design, which may have significantly affected the outcome or statistical analysis.

Patients who were taking urate-lowering therapy (ULT) prior to the study completed screening procedures on day -30, at which time their ULT was ceased and gout prophylaxis treatment was commenced. All subjects (including those not taking prior ULT) had a day -4 study visit to determine their baseline serum urate level for qualification (≥ 8.0 mg/dL). Randomization to active treatment occurred on day 1 and all subjects began taking gout prophylaxis treatment with either colchicine 0.6 mg once daily or naproxen 250 mg twice daily. Gout prophylaxis was continued throughout the 6-month study period in all subjects unless toxicity occurred. If patients were taking prophylactic naproxen, they were prescribed concurrent lansoprazole 15 mg/day for prevention of NSAID associated peptic ulcers. Subjects with a baseline CrCl of < 50 mL/min were not to receive naproxen for gout prophylaxis. Study assessments were performed at baseline (day 1 visit), and at months 2, 4 and 6.

7.1.2.3.2. Inclusion and exclusion criteria

The study enrolled patients between the ages of 18 and 85 years with hyperuricaemia (defined as serum urate ≥ 8.0 mg/dL) at the day -4 visit, and a history or presence of gout according to the ACR criteria. The study aimed to recruit at least 35% of patients with mild (CrCl 60-89 mL/min) or moderate renal impairment (CrCl 30-59 mL/min) but a CrCl of < 30 mL/min by (Cockcroft-Gault estimation) was an exclusion criteria. Subjects were also excluded if they had secondary hyperuricaemia (for example due to a myeloproliferative disorder), history of excessive alcohol intake (≥ 14 drinks/week), malignancy within the last 5 years (other than basal cell carcinoma of the skin), hepatic dysfunction (serum transaminases > 1.5 ULN), active peptic ulcer disease, history of myocardial infarction or stroke, rheumatoid arthritis, pregnancy or lactating, or any other significant medical condition considered by the investigator that would interfere with the treatment safety. The chronic use of prednisolone ≤ 10 mg/day and short term use (defined as ≤ 4 weeks of continuous use) of higher doses were allowed. If a

patient was taking colchicine for gout flare prophylaxis, macrolides and ketolides were prohibited medicines. If a patient was taking naproxen for gout flare prophylaxis, clopidogrel use was prohibited. Other medicines not allowed after the day -4 visit included thiazide diuretics, indapamide, aspirin > 325 mg/day, losartan, azathioprine, mercaptopurine, cyclosporine, fenofibrate, theophylline, and sulfamethoxazole/trimethoprim.

7.1.2.3.3. *Study treatment, blinding and randomization*

Qualifying subjects were randomized 1:1:1 by a computer generated program into 1 of 3 treatment groups: FBX 40 mg once daily (given as 2 x 20 mg tablets), FBX 80 mg once daily (given as 4 x 20 mg tablets) or allopurinol once daily (300 mg/day if CrCl at least 60 mL/min; or 200 mg daily if baseline CrCl between 30 and 59 mL/min; given as 100 mg tablets). The doses of allopurinol used in this trial (200-300 mg/day, depending on renal function) are consistent with contemporary treatment guidelines (Stamp et al, 2012). The Abbott formulation of FBX tablets was used in this trial. All patients received 1 capsule of study medication (FBX or allopurinol) daily, to be taken in the morning with gout prophylaxis drugs. Active study medication was over-encapsulated as a single capsule to maintain blinding. Gout prophylaxis medicines were not blinded.

Randomization was stratified by baseline renal function, and whether or not the subjects completed 1 of the 2 OLE studies (TMX-##-005 or C##-021). The 4 strata in the study were:

- Subjects with normal renal function or mild renal impairment, and who completed either Study TMX-##-005 or C##-021,
- Subjects with moderate renal impairment, and who completed either Study TMX-##-005 or C##-021,
- Subjects with normal renal function or mild renal impairment, who did not participate in either Study TMX-##-005 or C##-021, and
- Subjects with moderate renal impairment, who did not participate in either Study TMX-##-005 or C##-021.

7.1.2.3.4. *Efficacy measures*

The primary efficacy variable in Study F-GT##-153 was the proportion of subjects in each treatment group whose serum urate level decreased to < 6.0 mg/dL at the final visit (6 months). In addition, the responder rates were summarized by subgroups of interest at baseline: serum urate level (< 9.0 mg/dL, 9.0- < 10 mg/dL and \geq 10.0 mg/dL), gender, race, age (< 45, 45- < 65, \geq 65 years), renal function (normal, mildly impaired, or moderately impaired), prior use of ULT (yes/no), BMI, and tophus present (yes/no) at entry.

Secondary efficacy endpoints in Study F-GT##-153 were:

- Proportion of subjects with renal impairment whose serum urate decreased to < 6.0 mg/dL at the final visit,
- Proportion of subjects whose serum urate decreased to < 6.0 mg/dL, < 5.0 mg/dL and < 4.0 mg/dL at each visit, and
- Mean percentage reduction from baseline in serum urate level, and
- Incidence of gout flares during the study.

7.1.2.3.5. *Statistical methods and sample size*

The primary and all secondary efficacy analyses were performed on the ITT population, which was defined as all randomized subjects who took at least 1 dose of study drug and who had baseline serum urate level \geq 8.0 mg/dL. One subject (in the allopurinol group) had a baseline serum urate level < 8.0 mg/dL, and was excluded from the ITT population. Patients who

received either dose of allopurinol dose (200 mg or 300 mg/daily) were analysed together as a single pooled group.

The primary comparison of the primary efficacy variable was between FBX 40 mg/day and allopurinol. This comparison was made using a closed testing procedure within 2 steps. The first test was for non-inferiority using a 2-sided 95% CI of the difference in proportion of responders. If step 1 was achieved, then a second test for superiority between the 2 groups was performed using Fisher's exact test. FBX 80 mg/day was also compared to allopurinol and FBX 40 mg/day using Fisher's exact test. The association between each subgroup variable and the serum urate response was tested using a logistic regression model. The same statistical approach as described above was undertaken for all of the secondary efficacy analyses apart from the percentage of reduction from baseline in serum urate level, which was tested at each visit using a 1-way ANOVA method.

A total of 2250 subjects (750 per treatment group) were planned to be enrolled in the study.

The sample size would provide:

- At least 90% power to meet the non-inferiority criteria between FBX 40 mg/day and allopurinol for the primary efficacy measure,
- At least 90% power to detect a 10% difference between FBX 40 mg/day and allopurinol for the primary efficacy variable, and
- At least 90% power to detect a 10% difference for the secondary efficacy comparison between FBX 40 mg and 80 mg daily.

For the determination of non-inferiority it was anticipated that the response rate for the primary efficacy outcome would be 50% for both the FBX 40 mg and allopurinol groups (based on the FBX 40 mg results observed in Study TMX-##-004, and the results for allopurinol seen in Studies C##-009 and C##-010).

7.1.2.3.6. *Subject disposition and protocol deviations*

A total of 3609 subjects were screened and 2269 subjects were randomized in Study F-GT##-153 (219 under the original protocol, 1459 under amendment 1, and 591 after the implementation of amendment 2). The commonest reasons for screen failure ($n = 1340$; 37.1% of 3609) were serum urate level < 8.0 mg/dL at baseline (54% of screen failures), withdrawal of consent (10% of screen failures) and significant concurrent medical condition (6% of screen failures). Of the 2269 patients randomized into the trial, 757 were allocated to the FBX 40 mg/day group, 756 were randomized to FBX 80 mg/day and 756 subjects were randomized to receive allopurinol. Apart from 1 patient in the allopurinol arm who had a baseline serum urate level of < 8.0 mg/dL (7.6 mg/dL), all of the randomized patients received at least 1 dose of study medication and were included in the ITT population for the efficacy analyses. In the allopurinol group, 145 subjects received allopurinol 200 mg/day and 611 received allopurinol 300 mg/day. Seven subjects with a CrCl in the range of ≥ 20 to < 80 mL/min were randomized to receive allopurinol 200 mg/day under the original protocol, but those subjects would have been randomized to receive allopurinol 300 mg/day according to criteria for allopurinol dosing in subjects with mild renal impairment (CrCl 60-89 mL/min) in protocol amendment 1. However, these subjects were randomized correctly according to the original protocol criteria at the time of recruitment.

A total of 418 subjects (18.4% of 2269) prematurely discontinued from the study: 16.5% (125/757) of patients in the FBX 40 mg group, 20.9% (158/756) of subjects in the FBX 80 mg arm, and 17.9% (135/756) of patients in the allopurinol group. The most frequently reported primary reason for premature discontinuation was AEs (7.7%; 174/2269), followed by lost to follow-up (3.9%; 89/2269). Of the 418 patients who prematurely discontinued from the trial, 120 (28.7% of 418) did so within the first month on treatment.

Potentially important protocol deviations in this study were categorized according to the following criteria: subjects who did not meet inclusion/exclusion criteria but were enrolled in the study; subjects who developed withdrawal criteria but were not withdrawn; subjects who received excluded concomitant medications; and subjects who received the wrong dose or treatment. Protocol deviations were matched in type and incidence between the 3 treatment groups.

7.1.2.3.7. *Baseline data*

Demographic data for the 2269 subjects involved in Study F-GT##-153 were similar between the treatment arms with no observed statistically significant differences. The mean age ranged from 52.5 years to 53.0 years across the treatment groups (minimum to maximum range: 19-85 years). In all of the treatment groups, subjects were predominately Caucasian (82.1%; 1863/2269) and male (94.4%; 2141/2269). The mean BMI was 32.8 kg/m², and 63.6% (1442/2269) of subjects had BMI \geq 30 kg/m² (range: 16-64 kg/m²). The majority of subjects (68.3%; 1549/2269) were alcohol drinkers, and either non-or ex-tobacco users (81.9%; 1859/2269).

As required by the protocol, all subjects had a history or presence of gout at baseline, and were to have a serum urate level of \geq 8.0 mg/dL at the day -4 Visit. The majority of subjects (63.1%; 1432/2269) had a baseline serum urate level \geq 9.0 mg/dL. The mean baseline serum urate level ranged from 9.5 mg/dL to 9.6 mg/dL across the 3 treatment groups. Overall, the mean time since gout diagnosis was 11.6 years (median 9.4 years). Just over half of all subjects (54.4%; 1234/2269) had experienced an acute gout flare within 2 months prior to the study commencement. A small proportion of patients (11.6%-12.9% of subjects across the 3 treatment groups) had participated in the Phase III study program (Studies TMX-##-005 or C##-021) prior to this trial.

The majority of subjects (65.4%; 1483/2269 subjects) had mild-to-moderate renal impairment. At baseline, 57.2% of subjects (1297/2269) had a history of cardiovascular disease. The percentages of subjects with a history of cardiovascular disease ranged from 55.6% to 57.9% across the treatment groups. The most common (> 5% of all subjects) cardiovascular medical conditions at baseline were hypertension (52.8%), cardiac arrhythmia (10.2%), and coronary artery disease (8.5%). No statistically significant differences were observed across treatment groups in the percentage of subjects with history of cardiovascular disease. In addition, 13.8% (312/2269) had a history of diabetes and 41.5% (942/2269) had a history of hyperlipidaemia. Despite the cardiovascular risk factor profile of the cohort, only 20.8% (471/2269) of subjects were taking anti-thrombotic drugs (mostly, low dose aspirin [17.8%]) at baseline. The majority of patients (79.6%; 1807/2269) received low dose colchicine for gout prophylaxis with similar proportions of use (78.6%-80.7%) across the 3 treatment groups. Naproxen 250 mg twice daily with lansoprazole was taken by 15.2% (346/2269) of patients and 5.1% (116/2269) received another gout prophylaxis therapy (celecoxib, indomethacin, or prednisolone).

7.1.2.3.8. *Efficacy results*

The proportions of subjects achieving a serum urate level < 6.0 mg/dL at the final study visit were 45.2% (342/757) for FBX 40 mg, 67.1% (507/756) for FBX 80 mg and 42.1% (318/755) in the allopurinol group. Analysis determined FBX 40 mg/day to be non-inferior to allopurinol. The treatment difference between the FBX 40 mg and allopurinol groups was 3.1%, which was not statistically significant. The differences in the response rate between FBX 80 mg versus FBX 40 mg was 21.9%; and for allopurinol was 24.9%. Both of the pair-wise comparisons of FBX 80 mg versus either of the other 2 treatment groups were statistically significant ($p < 0.001$).

In addition, subgroup analyses for proportions of subjects whose final visit serum urate level was < 6.0 mg/dL were summarized for the following factors; age, gender, race, treatment duration (that is month 2, 4, and 6), baseline serum urate level, presence of tophi, whether the subject finished Study TMX-##-005 or C##-021, prior use of ULT, tobacco use, BMI, and renal

function. In all of the subgroup analyses, the comparisons between treatment groups were consistent with the overall analysis, that is response rates in the FBX 80 mg treatment group were statistically significant higher than the FBX 40 mg and allopurinol treatment groups; and the response rates were not statistically significant different between the FBX 40 mg and allopurinol treatment groups. In addition to the above subgroup analyses, subjects in all 3 treatment groups who had completed one of the long-term FBX studies (TMX-##-005 or C##-021) had significantly higher response rates than newly recruited patients. However, there was no statistically significant interaction for this factor (that is prior FBX study involvement) by treatment group.

Results according to baseline renal function were a particular outcome of interest in this study. The proportions of subjects with mild-to-moderate renal impairment who achieved a serum urate level < 6.0 mg/dL at the final visit was 49.7% (238/479) for FBX 40 mg, 71.6% (360/503) for FBX 80 mg, and 42.3% (212/501) in the allopurinol groups. Among the subjects with mild-to-moderate renal impairment, a statistically significant higher proportion of subjects in the FBX 40 mg group had a final serum urate < 6.0 mg/dL compared to allopurinol ($p = 0.021$). In addition, the proportion of subjects with mild-to-moderate renal impairment who achieved a serum urate level of < 6.0 mg/dL in the FBX 80 mg group was statistically higher compared to both the FBX 40 mg ($p < 0.001$) and allopurinol treatment groups ($p < 0.001$). Across all treatment arms, response rates for subjects with mild renal impairment were higher than the response rates for subjects with either moderate renal impairment, or normal renal function. Statistical analysis of this observation revealed a significant interaction between treatment and baseline renal function ($p = 0.021$). Response rates for both the FBX 40 mg and 80 mg groups were higher for subjects with moderate renal impairment compared to FBX treated subjects with normal renal function; while among subjects who received allopurinol, response rates were higher for subjects with normal renal function (41.7%) compared to subjects with moderate renal impairment (31.6%).

When response was evaluated by the proportions of subjects who achieved a serum urate level of < 6.0 mg/dL at each visit, a statistically significantly higher proportion of subjects in the FBX 40 mg group had a final serum urate level of < 6.0 mg/dL at the month 2 visit compared to allopurinol ($p < 0.031$). The proportions of subjects in the FBX 40 mg group who achieved a serum urate level < 6.0 mg/dL at subsequent visits were higher than those of the allopurinol group; however, these differences were not statistically significant. A significantly higher proportion of subjects on FBX 80 mg group achieved a serum urate level of < 6.0 mg/dL at each visit, compared to subjects in either the FBX 40 mg or allopurinol group.

A significantly higher proportion of subjects in the FBX 40 mg group compared to the allopurinol group achieved a serum urate level of < 5.0 mg/dL at the month 2 (15.4% [108/703] versus 11.7% [80/685]; $p < 0.05$) and month 6 Visits (19.3% [119/618] versus 13.2% [100/755]; $p < 0.05$). A significantly higher proportion of subjects in the FBX 80 mg group achieved a serum urate level of < 5.0 mg/dL at each scheduled visit, compared to subjects in either the FBX 40mg group or the allopurinol group. A significantly higher proportion of subjects in the FBX 80 mg group achieved a serum urate level < 4.0 mg/dL at each visit, compared to subjects in either the FBX 40 mg or the allopurinol group.

A statistically significant difference was noted in the mean percentage reduction in serum urate levels from baseline to the final visit in subjects who received FBX 40 mg compared to those who received allopurinol ($p = 0.05$). In addition, a statistically significant difference was noted in the mean percentage reduction in serum urate levels from baseline to each scheduled visit in subjects who received FBX 80 mg compared to those who received FBX 40 mg or allopurinol ($p < 0.001$).

The proportions of subjects who required treatment for gout flares during the study (day 1 through to month 6) were 31.3% (237/757) for the FBX 40 mg group, 31.1% (235/756) for the FBX 80 mg arm, and 24.6% (186/755) for the allopurinol groups. Apart from the pair-wise

between FBX 40 mg and allopurinol between 2-4 months, patients who received FBX (either dose) had a significantly higher proportion of acute gout flares requiring treatment (overall while on study medication, and at each 2-month study period) than subjects in the allopurinol treatment group.

7.1.3. Analyses performed across trials (pooled analyses and meta-analyses)

The sponsor has provided an integrated summary of efficacy whereby the data from the 2 pivotal Phase III studies (C##-009 and C##-010) is combined in a pooled analysis with the efficacy data from Study F-GT06-153. The integrated efficacy analysis provides additional data on 2 aspects of relevance in this submission:

- the incidence of gout flares observed when FBX 80 mg/day is administered with 6-months versus 8 weeks of gout flare prophylaxis,
- additional efficacy information in subjects with renal impairment.

7.1.3.1. *Gout flare*

In Study F-GT##-153 of 6 months duration, gout flare prophylaxis (colchicine or naproxen + lansoprazole) was given for at least 6 months as per the 2007 EULAR guidelines. The proportions of patients requiring treatment for gout flares were similar between the FBX 40 and 80 mg groups throughout the study at 31% (19-20% months 0-2, 13-15% months 2-4, and 13% months 4-6). In Studies C##-009 and C##-010, gout flare prophylaxis (naproxen or colchicine) was given for only 8 weeks. During Study C##-009, more than half of subjects required treatment for gout flare before week 28 ((ranging from 51-66%). Similar findings were recorded in Study C##-010, whereby 64-72% of all subjects across the treatment groups required treatment for gout flare by 52 weeks. This data highlights that prophylactic treatment with NSAID or colchicine for up to 6 months with initiation of FBX therapy (any dose between 40-120 mg/day) is recommended.

7.1.3.2. *Serum urate reduction in subjects with renal impairment*

In Study F-GT##-153, patients with renal impairment were included in a prospective manner and treatment randomisation was stratified on baseline estimated CrCl. FBX 80 mg/day was statistically more effective in lowering serum urate levels < 6.0 mg/dL than allopurinol (200-300 mg/day) and FBX 40 mg/day in subjects with mild or moderate renal impairment. Similar results were observed in Study C##-009 whereby a total of 40 subjects had a baseline serum creatinine level between 1.5 and 2.0 mg/dL. Serum urate response rates (< 6.0 mg/dL) were 44% (4/9) with FBX 80 mg, 45% (5/11) with FBX 120 mg, 60% (3/5) with FBX 240 mg and zero for allopurinol 100 mg/day.

7.2. *Evaluator's conclusions on clinical efficacy for "Treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history of, or presence of, tophus and/or gouty arthritis).*

The sponsor has provided the efficacy data from 2 pivotal, randomized, multicentre, double blind trials (C##-009 and C##-010) to support the efficacy of FBX in treating adult patients with hyperuricaemia and gout. Supportive evidence of efficacy is provided by another Phase III study (F-GT##-153) of 6-months duration, as well as 2 long-term, open-label extension trials (TMX##-005 and C##-021) plus a 28-day Phase II dose-finding study (TMX##-004). In general, the trials were of adequate design to evaluate the proposed indication, and they had a clear and appropriate plan of analysis. The biologic rationale for the use of FBX in hyperuricaemia is clear (as a XO inhibitor), and the doses explored in the clinical study program (ranging from 40-240 mg/day) is appropriate to define the registered dose. Active comparator therapy (allopurinol 100-300 mg/day) was consistent with contemporary literature, including international

treatment guidelines. In addition, patients received appropriate gout prophylaxis therapy (NSAID or colchicine for most subjects).

In Study C##-009, a total of 1072 subjects were randomized to 5 treatment groups consisting of placebo (n = 134), FBX 80 mg/day (n = 267), FBX 120 mg/day (n = 269), FBX 240 mg/day (n = 134) or allopurinol 100/300 mg/day (n = 258) for 28 weeks of treatment follow-up. In Study C##-010, a total of 760 patients were randomized to receive FBX 80 mg/day (n = 256), FBX 120 mg/day (n = 251) or allopurinol 300 mg/day (n = 253) for 52 weeks of treatment follow-up. The majority of patients (at least 61%) in all treatment groups completed the 28-52 weeks of follow-up in both pivotal studies. A relatively low proportion of major protocol violations or deviations (< 10%) occurred in both pivotal Phase III studies, with equal incidence among the treatment groups.

The populations examined in the Phase III studies are similar in demographics to patients that would be treated in Australian clinical practice. The trials were conducted mainly in the USA, and mostly recruited overweight, middle-aged Caucasian men. The background treatments (overall, as well as for gout flare prophylaxis) are consistent with Australian treated patients, and the incidence and pattern of co-morbid illness was to be expected. The baseline disease characteristics of the study cohorts are consistent with a group of patients with significant hyperuricaemia and evidence of urate deposition, which is congruent with the proposed indication wording. However, the generalizability of the study results to a broader population in Australia has limitations. As stated in the RMP for Australia, the trials have excluded certain patient subgroups at risk of hyperuricaemia such as those with significant over-production of urate and organ transplant recipients, and there is an under-representation of patients with significant renal or hepatic impairment.

The primary efficacy outcome in the 2 pivotal Phase III studies was the proportion of subjects who at the final study visit achieved a consistent reduction in serum urate level to < 6.0 mg/dL. This is an appropriate efficacy measure for determining the utility of a therapy in treating symptomatic hyperuricaemia. There were also several other secondary efficacy endpoints in both studies, some of which were dependent on subjective assessments done by either the subject (for example various quality of life instruments). Nonetheless, the efficacy endpoints were appropriate for evaluating the proposed indication for FBX.

The primary efficacy endpoint in the 2 pivotal Phase III trials was achieved. At 28 weeks in Study C##-009, the proportion of subjects whose last 3 serum urate levels were < 6.0 mg/dL were 0% in the placebo group, 48.1% (126/262) in the FBX 80 mg arm, 65.1% (175/269) in the FBX 120 mg group, 68.7% (92/134) in the FBX 240 mg cohort, and 22.4% (60/268) in the allopurinol group. Each of the FBX treatment groups and the allopurinol therapy arm were statistically superior to placebo. The 97.5% CIs for the differences in response rates between FBX 80 mg versus allopurinol were 16.7%-34.7% (p < 0.001); and for FBX 120 mg versus allopurinol were 34.0%-51.3% (p < 0.001), thus demonstrating the non-inferiority of both FBX 80 mg/day and 120 mg/day relative to allopurinol 300/100 mg daily. The proportion of subjects in Study C##-010 (52 weeks duration) whose last 3 serum urate levels were < 6.0 mg/dL were 53.3% (136/255) in the FBX 80 mg group, 61.6% (154/250) in the FBX 120 mg arm and 21.1% (53/251) in the allopurinol group. The 97.5% CIs for the differences in response rates for FBX 80 mg versus allopurinol were 23.1% and 41.3%; and for FBX 120 mg versus allopurinol were 31.5% and 49.5%. This result demonstrated the non-inferiority of each FBX dose relative to the allopurinol 300 mg/day. Additionally, the differences between each of the FBX treatment groups (32% difference for FBX 80 mg and 41% difference in proportions for 120 mg) and allopurinol confirmed that each FBX dose was statistically superior to allopurinol (p < 0.001 for both comparisons). The difference in response between the FBX 80 mg and 120 mg treatment groups was not statistically significant. Various sensitivity analyses confirmed the robustness of the primary statistical analysis. Exploration of patient factors upon the primary efficacy response was unrevealing apart from showing that patients with very high serum urate

levels at baseline (> 10.0 mg/dL) had a slightly lower overall rate of response (regardless of treatment option).

The results for the secondary efficacy endpoints were consistently observed. In the both pivotal Phase III studies, all of the secondary efficacy outcomes associated with changes in serum urate (for example proportion of subjects reaching serum urate level of < 5.0 and < 4.0 mg/dL, and the mean percentage reduction in serum urate from baseline) demonstrated a treatment difference with FBX. However, either inconsistent or no effect with FBX was demonstrated for the percentage reduction in primary tophus size or the total number of tophi. In addition, the percentage of patients requiring treatment for an acute gouty arthritis flare, particularly during the first 8 weeks of therapy, was higher in the FBX treatment groups compared to allopurinol and placebo. The quality of life measurements demonstrated inconsistent comparative results between the active treatment groups with some parameters appearing to be worse in those receiving FBX versus allopurinol.

Study F-GT##-153 is supportive of the key efficacy findings of the 2 pivotal trials by demonstrating:

- A statistically higher proportion of subjects treated with FBX 80 mg/day (67.1%; 507/756) achieving a serum urate level of < 6.0 mg/dL at final study visit (26 weeks) compared to 45.2% (342/757) of patients in the FBX 40 mg/day group, and 42.1% (318/755) of subjects (82%) in the allopurinol group. In addition, FBX 40 mg/day was non-inferior to allopurinol for this primary outcome measure with the absolute treatment difference being 3.1%.
- A statistically higher percentage of patients treated with FBX 80 mg/day achieved a serum urate level of < 5.0 and < 4.0 mg/dL at each scheduled visit (bimonthly) compared to those who received treatment with either FBX 40 mg/day or allopurinol 200-300 mg/day.
- The proportions of subjects with mild-to-moderate renal impairment who achieved a serum urate level < 6.0 mg/dL at the final visit was 49.7% (238/479) for FBX 40 mg, 71.6% (360/503) for FBX 80 mg, and 42.3% (212/501) in the allopurinol groups. Among the subjects with mild-to-moderate renal impairment, a statistically significant higher proportion of subjects in the FBX 40 mg group had a final serum urate < 6.0 mg/dL compared to allopurinol ($p = 0.021$). In addition, the proportion of subjects with mild-to-moderate renal impairment who achieved a serum urate level of < 6.0 mg/dL in the FBX 80 mg group was statistically higher compared to both the FBX 40 mg ($p < 0.001$) and allopurinol treatment groups ($p < 0.001$).
- However, a statistically higher percentage of patients in each of the FBX treatment groups required treatment for a gout flare during the 6-month study (31.3% [237/757] for the FBX 40 mg group, and 31.1% [235/756] for the FBX 80 mg arm) compared to 24.6% (186/755) of subjects in the allopurinol arm.

The long-term, open-label extension studies (TMX-##-005 and C##-021) allowed participants who completed the forerunner studies to continue to receive FBX (as per the double blind period), or be switched to FBX from allopurinol. Most of the treatment switch patients (for example 67.1% [55/82] of subjects in Study C##-021) achieved an improvement in their serum urate levels similar to that for the subjects initially treated with FBX, while many of those who continued to take FBX maintained their response (71-80% at a further 6 months of follow-up in Study C##-021). In Study TMX-##-005, the ability of FBX to effectively lower and maintain a serum urate level of < 6.0 mg/dL was demonstrated in 78.2% (68/87) of subjects at 1 year, 76.1% (54/71) of patients at 2 years, 83.6% (56/67) of subjects at 3 years and 90.2% (55/61) of subjects at 4 years. The majority of subjects who continued long-term FBX treatment were taking 80 mg/day. After the first year of FBX treatment in Study TMX-##-005, less than 10% of all subjects received treatment for a gout flare. The overall incidence of gout flares gradually declined over 5 years with continued FBX treatment, with the greatest reduction noted in the patient group receiving 80 mg/day.

Study TMX-##-004 was a Phase II, dose-finding trial, which informed the selection of FBX doses (80 and 120 mg once daily) chosen for examination in the 2 pivotal Phase III studies (C##-009 and C##-010). After 28 days of treatment, the mean percentage reduction in serum urate level (by enzymatic method) was 2.15% for placebo, 36.6% for FBX 40 mg/day, 44.3% for FBX 80 mg/day and 59.1% for FBX 120 mg/day. In addition, the proportion of hyperuricaemic patients achieving a serum urate level of < 6.0 mg/dL (by enzymatic method) in Study TMX-##-004 was greater in each of the FBX treatment groups (55.9% [19/34] in those treated with FBX 40 mg/day, 75.7% [28/37] for FBX 80 mg/day and 94.1% [32/34] for patients receiving FBX 120 mg/day) compared to zero patients who received placebo therapy.

In summary, the data in this submission supports the efficacy of FBX in treating adult patients with hyperuricaemia and gout, particularly with respect to the proportion of patients able to achieve a clinically significant reduction in their serum urate level (< 6.0 mg/dL). The 2 pivotal Phase III studies, as well as an additional Phase III trial (F-GT##-153) have adequately assessed the dose of FBX to be used in clinical practice (40-120 mg once daily) over an appropriate time frame of follow-up (26-52 weeks), and compared the relative effect of FBX to alternative treatment approaches such as allopurinol and placebo. The long-term, open-label experience provides sufficient information on the durability of response for up to 5 years of FBX treatment.

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies provided safety data for this evaluation:

8.1.1. Pivotal efficacy studies

In the pivotal efficacy studies (C##-009 and C##-010) the following safety data was collected:

General Adverse Events (AEs) were assessed by AE reporting and clinical assessment performed during the run-in period of up to 14 days, day 1, week 2 and 4, and every 4 weeks thereafter for up to 28 weeks in Study C##-009, and for up to 52 weeks in Study C##-010.

Skin rash and hypersensitivity reactions were an AE type of special interest because of the known association with allopurinol treatment (active comparator). This type of AE was assessed by its overall number of events, severity and their relationship to study treatment.

Laboratory tests, including haematology and blood chemistry were performed at baseline, and every 4 weeks thereafter in each study. Thyroid function tests were done at baseline and every 24 weeks, as well as at the final study visit in both pivotal trials.

Electrocardiogram (ECG) was performed at baseline (day -2), and week 24-28 and 52 (in Study C##-010), or upon early withdrawal (at any time point).

AE reporting was standardised by the sponsor for analysis by assigning preferred terms as set out in the Medical Dictionary for Regulatory Activities (MedDRA) version 7.0. All AEs were summarized by System Organ Class (SOC), high level term and preferred term; graded according to the National cancer Institute's Common Terminology Criteria; and had their relationship to treatment assessed.

Pivotal studies that assessed safety as a primary outcome.

There were no studies that assessed safety as the primary outcome.

8.1.2. Dose-response and non-pivotal efficacy studies

The FBX dose-response study (TMX-##-004) and the non-pivotal efficacy Study F-GT##-153 provided safety data. In addition to the controlled trials, there were 2 long-term OLE studies

(TMX-##-005 and C##-021), which contributed safety data. The safety information from the 2 long-term, open-label trials will be presented together in this report.

Adverse cardiovascular (CVS) outcomes was a safety issue of special interest in Study F-GT##-153 as the 2 preceding Phase III studies (identified as pivotal in this submission) showed a higher incidence of CVS related AEs in the FBX treatment groups compared to allopurinol and placebo. The main CVS safety variables were:

- Antiplatelet Trialists' Collaboration (APTC) criteria, which includes non-fatal myocardial infarction, non-fatal stroke and cardiovascular death, as well as
- Non-APTC Cardiovascular Events – unstable angina, coronary or cerebral revascularization, transient ischaemic attack, congestive heart failure, arrhythmia (in the absence of myocardial ischaemia) and venous and peripheral arterial vascular thrombotic events.

Cardiovascular AEs were analysed according to investigator reported events, and then also by an independent expert adjudication committee. A planned sample size of 2250 subjects (750 per treatment group) would provide a 90% and 80% probability to expect that the observed relative risk of an adjudicated APTC event for either of the FBX dose groups to allopurinol is no greater than 2.344 and 1.750, respectively. The APTC event rate was estimated to be 0.6% for both FBX treatment groups and allopurinol, based on the observed data in the Phase III studies (combined event data for FBX 80 mg, 120 mg and 240 mg/day).

8.1.3. Other studies evaluable for safety only

In total, 25 Phase I clinical pharmacology studies provided safety data in this submission including: TMX-##-001, TMX-##-002, TMX-##-003, TMX-##-006, TMX-##-008, TMX-##-009, TMX-##-010, TMX-##-012, TMX-##-014, TMX-##-016, TMX-##-017, TMX-##-018, C##-005, C##-006, C##-013, C##-023, C##-033, C##-034, C##-036, C##-040, C##-044, C##-054, C##-057, C##-059 and F-P1##-162.

8.2. Patient exposure

A total of 4072 subjects received at least 1 dose of FBX in the Phase I, 2 and 3 clinical studies with the mean duration of FBX dosing being 362 days. Across the Phase I, II and III studies, a total of 2468 subjects were exposed to FBX 80 mg once daily and 1079 subjects were exposed to FBX 120 mg once daily, which are the requested doses in this submission. The duration of dosing (mean + range) in the FBX 80 mg/day treated subjects was 187 (1-1274) days and for the patients who received 120 mg/day was 201 (1-1675) days.

In the Phase I studies, 811 otherwise healthy subjects received at least 1 dose of FBX (ranging from 10-300 mg daily), and 489 of these subjects received FBX for at least 7 days duration.

In the Phase III trials, the overall exposure to study medication was comparable in the FBX 80 mg/day (n = 1279 subjects treated for a mean duration of 184 days) and allopurinol treatment groups (n = 1277 patients treated for a mean duration of 192 days); but lower than in the FBX 120 mg/day (n = 520 patients treated for a mean duration of 214 days). The FBX 240 mg/day (n = 134 subjects treated for a mean duration of 147 days) and placebo arms (n = 134 subjects treated for a mean duration of 163 days) had much lower overall exposure than the 3 preceding active treatment groups, as both of those treatment strategies were not included in the 52-week Study C##-010. The exposure to FBX 80 mg and 120 mg once daily in the studies supporting this application exceeds the minimum exposure recommendations provided in the International Conference on Harmonisation (ICH) E1A for the safety evaluation of drugs intended for long-term treatment.

In the long-term OLE studies (C##-021 and TMX-##-005) a total of 1143 subjects have received at least 1 dose of FBX for a mean exposure period of 850 days (representing 2661 PY of exposure), which is a much greater exposure than for subjects treated with allopurinol (178

subjects treated for an average of 353 days). This imbalance is primarily a result of study design whereby switching between treatment groups (mainly from allopurinol to FBX) was allowed based on satisfactory therapeutic response. In terms of the FBX exposure in the long-term OLE trials by dose: 917 patients took 80 mg/day for a mean of 695 days (1746 PY of exposure), 524 subjects took 120 mg/day for a mean of 612 days (878 PY of exposure) and 12 patients took 40 mg/day for a mean of 1146 days (38 PY of exposure). In total, 909 subjects (579 on 80 mg, 315 on 120 mg and 8 on 40 mg/day) have taken FBX continuously for > 12 months on the OLE trials, 55 of whom (39 on 80 mg, 10 on 120 mg and 6 on 40 mg/day) have taken therapy for > 60 months. In the allopurinol treated patients, 56 of the original 178 cohort (71.8%) took treatment for > 12 months, but no subjects continuously took therapy beyond 42 months of follow-up in the OLE studies.

8.3. Adverse events

8.3.1. All adverse events (irrespective of relationship to study treatment)

8.3.1.1. Pivotal studies

8.3.1.1.1. Study C##-009

The total number of subjects in each treatment group who reported at least 1 Treatment-Emergent Adverse Events (TEAEs) was 67.8% (181/267) in the FBX 80 mg group, 68.0% (183/269) in the FBX 120 mg arm, 74.6% (200/268) in the allopurinol group, 73.1% (98/134) in the FBX 240 mg arm and 72.4% (97/134) in the placebo group. The most commonly reported TEAEs ($\geq 5\%$ incidence in any treatment group) were upper respiratory tract infection (16-20%), non-infective diarrhoea (6-13%), musculoskeletal pain (9-10%), headache (5-9%) and hypertension (1-6%). Most adverse events were mild to moderate in severity.

Statistically significant differences were observed for the following treatment comparisons:

- FBX 240 mg group compared to each of the 3 other active treatment groups (FBX 80 mg, FBX 120 mg, and allopurinol) for the incidence of non-infective diarrhoea (13% versus 6-7%); and for the incidence of neurological signs and symptoms (7% versus 2% in all 3 other active treatment arms);
- Allopurinol cohort compared to the placebo and FBX 80 mg groups for the incidence of hypertension (1% versus 5-6%); and
- Placebo compared to each of the active treatment groups (FBX 80 mg and 120 mg QD, and allopurinol) for the incidence of muscle related signs and symptoms (5% versus $\leq 1\%$).

On a preferred term level for evaluating TEAEs, numerical differences in the incidences between treatment groups were statistically significant for nausea (4.5% [6/134] in the FBX 240 mg group versus < 1% [2/268] for allopurinol) and for nasopharyngitis (11.9% [16/134] in the FBX 240 mg group versus 4.9% [13/268] in the allopurinol arm). The incidences of all other individual types of TEAEs (by the preferred term level of assignment) were similar across groups.

Rash related TEAEs were an AE of special interest in the pivotal Phase III studies as allopurinol, the only other XO inhibitor currently in use, has been associated with potentially severe rash (for example hypersensitivity syndrome). The incidence of skin rash related TEAEs was similar in the placebo (2%), all FBX treatment groups (2-3%) and allopurinol treatment groups (2%). Apart from 1 case, the other rash related AEs were graded as either mild or moderate in severity. No FBX dose or time related trends were observed for the development of skin rash.

8.3.1.1.2. Study C##-010

The highest incidence of TEAEs was observed in the allopurinol 300 mg/day group (85.0%; 215/253) followed by the FBX 80 mg arm (80.1%; 205/256) and the FBX 120 mg group (75.3%;

189/251). The difference between the allopurinol and FBX 120 mg groups for the overall incidence of TEAEs was statistically significant ($p < 0.05$ using Fisher's exact test), but not clinically relevant.

The most commonly reported TEAEs ($\geq 5\%$ incidence in any treatment group) were upper respiratory tract infection (21-30%), musculoskeletal pain (14-15%), joint related symptoms and signs (13-15%), non-infective diarrhoea (6-11%), and headache (9% in all 3 groups). Most adverse events were mild to moderate in severity.

Using the MedDRA preferred terms dictionary for individual types of TEAEs, statistically significant differences were observed for the following treatment comparisons:

- FBX 120 mg group compared to FBX 80 mg for the incidence of upper respiratory tract infections (30% versus 21%); and for the incidence of infections not elsewhere classified (NEC)(2% versus 0); and
- FBX 80 mg compared to allopurinol for the incidence of nausea and vomiting (7% versus 3%).

In total, 28 (10.9% of 256) subjects in the FBX 80 mg group, 19 (7.6% of 251) patients in the FBX 120 mg arm, and 26 (10.3% of 253) subjects in the allopurinol group reported at least 1 rash related AE. The majority of skin rash AEs resolved while continuing treatment. No subject suffered a rash AE that was rated as serious.

8.3.1.2. Other studies

8.3.1.2.1. Study F-GT##-153

Overall, 56.1% of all subjects (1272/2269) experienced at least 1 TEAE in Study F-GT##-153. Occurrence rates did not differ among the treatment groups affecting 56.7% (429/757) of subjects in the FBX 40 mg group, 54.2% (410/756) of patients in the FBX 80 mg arm, and 57.3% (433/756) of subjects in the allopurinol group. The majority of TEAEs were mild or moderate in severity. The rates of the most frequently reported TEAEs were similar in the FBX 40 mg group, FBX 80 mg arm, and allopurinol group and included: upper respiratory tract infections (9.4%, 7.0%, and 7.5%, respectively), liver function test changes (8.3%, 6.9%, and 6.6%, respectively), non-infective diarrhoea (5.9%, 6.2%, and 7.5%, respectively), rash (5.8%, 5.6%, and 7.3%, respectively) and musculoskeletal and connective tissue signs and symptoms (5.7%, 5.0% and 4.2%, respectively).

A statistically significantly higher proportion of subjects in the allopurinol group than in the FBX 40 mg group experienced gastrointestinal upset (flatulence, bloating, and abdominal distension); muscle-related signs and symptoms; and nasal congestion. A statistically significantly higher proportion of subjects in the allopurinol group than in the FBX 80 mg group experienced dental and oral soft tissue infections, muscle-related signs and symptoms, and dermatitis and eczema. In the FBX 40 mg group, a statistically significantly higher proportion of subjects experienced neurological signs and symptoms than in the allopurinol group; and the FBX 40 mg patients experienced more dermal and epidermal AEs than the FBX 80 mg group.

There was no statistically significant difference in TEAEs between treatment groups for subjects with normal or abnormal renal function, or according to gout prophylaxis therapy (colchicine versus naproxen/lansoprazole).

8.3.1.2.2. Study TMX##-004

The number of subjects in each treatment group who experienced at least 1 AE was similar between the placebo (50%; 19/38) and the FBX treatment arms (54% [20/37] in the FBX 40 mg group, 58% [23/40] in the FBX 80 mg arm, and 50% [19/38] in the FBX 120 mg group). The majority of the AEs reported were mild or moderate in severity. There were no statistically significant differences between each FBX treatment group and placebo in the overall incidence of AEs or in the incidence of any specific type of AE. However, diarrhoea was observed more

frequently in the FBX 80 mg group treatment group (20%; 8/40) compared with the placebo, FBX 40 mg and FBX 120 mg treatment groups (11% [4/38], 3% [1/37] and 11% [4/38], respectively).

During this study, 10 subjects developed rash or allergy related AEs. One subject developed angioedema involving the upper lip after receiving FBX 120 mg/day and prophylactic colchicine for 7 days. The subject prematurely discontinued from the study. Another subject developed a rash on back, buttocks, and inner thigh on study day -2 (that is while on colchicine 0.6 mg twice daily before FBX was started). The rash resolved with topical hydrocortisone. The subject continued in the study and was randomized to FBX 120 mg/day without recurrence of rash. Another 2 subjects (skin breakdown around a tophus; and a skin reaction due to urinary incontinence) had intervention for their rashes, but continued their study medication. The other 6 subjects who developed rashes during the trial had self-limiting events that resolved without specific intervention and all continued in the study.

8.3.1.2.3. *Long-term OLE studies*

The overall percentage of patients who experienced TEAEs in Studies C##-021 and TMX-##-005 were higher in the FBX treatment groups (91.7% [11/12] for 40 mg, 74.3% [676/910] for 80 mg and 68.8% [359/522] for 120 mg) compared to the allopurinol group (56.7%; 101/178). However, when the overall number of TEAEs was adjusted for PY of exposure to medication it was similar between the allopurinol (207.8 AEs per 100 PY) and FBX 120 mg groups (199.7 AEs per 100 PY), but remained numerically higher in the lower FBX dose arms (242.1 AEs per 100 PY for FBX 80 mg, and 269.8 AEs per 100 PY for FBX 40 mg/day). The pattern of recorded individual types of AEs did not significantly alter with time in the long-term OLE trials compared to the controlled periods of the same studies. Most TEAEs were rated mild or moderate in severity, and were not considered to be related to study medication by site investigators.

8.3.1.2.4. *Phase I studies*

Among the 811 subjects who received at least 1 dose of FBX in the Phase I studies, 416 (51.3%) reported at least 1 treatment-emergent AE, the majority of which were rated mild or moderate in intensity. In the single dose FBX trials, 37.5% (114/304) subjects experienced an AE; while in the multiple dose FBX studies, 59.6% (302/507) subjects reported at least 1 treatment-emergent AE.

The most commonly reported types of AEs during dosing with FBX were headache (16.2%; 131/811), nausea (8.1%; 66/811), dizziness (6.2%; 50/811), feeling hot (4.6%; 37/811), abdominal pain (4.6%; 37/811), diarrhoea (3.8%; 31/811), fatigue (3.1%; 25/811), and back pain (2.6%; 21/811).

8.3.2. **Treatment-related adverse events (adverse drug reactions)**

8.3.2.1. *Pivotal studies*

8.3.2.1.1. *Study C##-009*

The number of subjects in each treatment group experiencing TEAEs that was considered by the investigator to be treatment-related was: 31 (23.1% of 134) in the placebo group, 56 (21.0% of 267) in the FBX 80 mg arm, 49 (18.2% of 269) in the FBX 120 mg group, 39 (29.1% of 134) in the FBX 240 mg arm, and 44 (16.4% of 268) in the allopurinol group. The difference in incidence between the FBX 240 mg group, and the FBX 120 mg and allopurinol groups were statistically significant ($p < 0.05$).

The most common reported ($\geq 2\%$ in any treatment group) treatment-related AEs by MedDRA preferred terms were: diarrhoea (1-7%), nausea (< 1-4%), headache (0-4%), abdominal pain (< 1-4%), dizziness (< 1-4%), and abnormal liver function tests (< 1-3%). Regarding individual types of AEs, a statistically higher rate of non-infective diarrhoea was observed in the FBX 240

mg group (6.7%; 9/134) compared to the FBX 120 mg (1.9%; 5/269) and allopurinol groups (1.5%; 4/268). Nausea and vomiting, gastrointestinal/abdominal pain, and neurological signs and symptoms were also statistically more common in the FBX 240 mg group compared to allopurinol. Among subjects with a baseline creatinine < 1.5 mg/dL, the incidence and type of treatment-related AEs was similar to the pattern observed in the overall study population.

8.3.2.1.2. *Study C##-010*

The incidence of treatment-related TEAEs was similar in the FBX 80 mg (24.6%; 63/256), FBX 120 mg (23.9%; 60/251) and allopurinol 300 mg QD (22.5%; 57/253) treatment groups. No statistically significant differences were observed between the 3 treatment groups for the overall incidence of treatment-related TEAEs or for any specific treatment-related TEAE. The most commonly reported ($\geq 2\%$ in any treatment group) treatment-related AEs were: abnormal liver function tests (4-5%), non-infective diarrhoea (3% in all groups), constipation (2% in all groups), headache (1-3%), dizziness (1-2%) and nausea (1-2%). The majority of these TEAEs were transient, and rated mild or moderate in severity.

8.3.2.2. *Other studies*

8.3.2.2.1. *Study F-GT##-153*

Overall, 18.8% of all subjects (426/2269) experienced at least 1 AE that was considered by the investigator to be treatment-related. The percentage of subjects with at least 1 treatment-related AE were 18.2% (138/757) in the FBX 40 mg group, 18.1% (137/756) in the FBX 80 mg arm and 20.0% (151/756) in the allopurinol group. The most frequently reported ($\geq 2\%$ of subjects in any group) treatment-related AEs in the FBX and allopurinol groups was liver function test abnormalities (6.6% [50/757] in FBX 40 mg, 5.4% [41/756] in FBX 80 mg, and 4.6% [35/756] of subjects in the allopurinol group), and non-infective diarrhoea (2.6% [20/757] in FBX 40 mg, 2.8% [21/756] in FBX 80 mg and 3.4% [26/756] of subjects in the allopurinol group). There were no statistically significant differences across the 3 treatment groups for the most frequently reported treatment-related AEs.

When treatment-related AEs were evaluated by colchicine use, rates of liver function test abnormalities (7.5%, 5.9%, 4.5% for FBX 40 mg, FBX 80 mg, and allopurinol treatment groups, respectively) were similar to the rates in all subjects; however when the rates of liver function test abnormalities were evaluated for naproxen/lansoprazole use (2.5%, 1.9%, and 3.2% for FBX 40 mg, FBX 80 mg, and allopurinol treatment groups, respectively) they were significantly lower in all 3 treatment groups. The rates of treatment-related diarrhoea (excluding infective aetiology) were similar in subjects taking either colchicine (2.2%, 1.8%, and 2.7% for FBX 40 mg, FBX 80 mg, and allopurinol, respectively) or naproxen/lansoprazole (2.5%, 2.9%, and 4.8% for FBX 40 mg, FBX 80 mg, and allopurinol, respectively).

8.3.2.2.2. *Study TMX-##-004*

The incidence of patients experiencing treatment related AEs was comparable among the 3 FBX treatment groups (19% [7/37] in the FBX 40 mg, 25% [10/40] in the FBX 80 mg, and 16% [6/38] in the FBX 120 mg group), but numerically higher than placebo (8%; 3/38). Three subjects in the FBX 80 mg treatment group reported severe (but not serious) diarrhoea. All of the other cases of diarrhoea were rated as either mild or moderate. Treatment-related AEs of abnormal liver function tests were observed in 5% (2/37) in the FBX 40 mg group, 3% (1/40) in the FBX 80 mg arm and 3% (1/38) of subjects in the FBX 120 mg group, compared to no reports in the placebo group. All of these AEs of abnormal liver function tests were associated with the co-administration of colchicine.

8.3.2.2.3. *Long-term OLE studies*

The proportion of subjects who recorded treatment related AEs in Studies C##-021 and TMX-##-005 was higher in the FBX treatment groups (47.1% [5/12] for 40 mg, 14.7% [134/910] for 80 mg and 12.6% [66/522] for 120 mg) compared to the allopurinol group (8.4%; 15/178).

However, when the overall number of treatment related AEs was adjusted for PY of exposure to therapy it was similar between all 4 of the treatment groups: 15.2 AEs per 100 PY for FBX 40 mg, 19.1 AEs per 100 PY for FBX 80 mg, 16.2 AEs per 100 PY for FBX 120 mg, and 15.0 AEs per 100 PY for the allopurinol treatment arm. Most of the treatment related AEs were rated mild or moderate in severity. For all treatment groups, the overall incidence of treatment related AEs was lower in the long-term extension phase compared to the controlled study periods, primarily due to the reduced frequency of visits in the OLE trials. The most common individual types of AEs recorded in the long-term OLE studies (regardless of FBX dose) were various terms reflecting abnormalities of liver function tests (3-4% of subjects in each FBX groups as well as the allopurinol arm), diarrhoea (2-3% in each of the treatment groups), raised renal function tests (BUN and serum creatinine), hyperlipidaemia and nephrolithiasis.

8.3.2.2.4. *Phase I studies*

In the early phase clinical trials, a total of 259 (31.9% of 811) subjects reported at least 1 AE that was considered by the study investigator to be at least possibly related to FBX. In the single dose FBX trials, 15.8% (48/304) subjects experienced a treatment related AE; while in the multiple dose FBX studies, 41.6% (211/507) subjects reported at least 1 treatment-related AE. The pattern of individual types of AEs that were considered to be treatment related was similar to that observed for overall AEs. The most commonly reported types of AEs that were considered to be related to FBX in the Phase I studies were headache (12.6%; 102/811), nausea (7.4%; 60/811), dizziness (4.4%; 36/811), feeling hot (4.1%; 33/811), diarrhoea (3.5%; 28/811), abdominal pain (3.3%; 27/811) and vomiting (2.2%; 18/811). In the early phase studies, 0.7% (6/811) of subjects developed various types of skin rashes, and another 3 subjects complained of pruritus without overt rash.

8.3.3. Deaths and other serious adverse events

8.3.3.1. *Pivotal studies*

8.3.3.1.1. *Study C##-009*

No subject died during the course of this study. A total of 34 subjects (2 placebo, 11 FBX 80 mg, 9 FBX 120 mg, 5 FBX 240 mg and 7 allopurinol 300 mg/day) experienced SAEs during the study. No subject who received allopurinol 100 mg/day reported an SAE during the trial. All SAEs were considered to be either unrelated or unlikely to be related to study medication by the investigator with the exception of 1 report. A subject in the FBX 240 mg group experienced an SAE of renal impairment that the investigator considered to be probably related to FBX. The subject, who had a history of kidney stones, had completed the study and enrolled in the extension study when the results of his day 197 24-hour CrCl revealed decreased renal function. Approximately 4 months after the onset of the SAE, a nephrologist assessed the patient and determined that he had normal renal function.

Cardiovascular (CVS) events were the most commonly observed SAEs and included chest pain (n = 4; 2 in the FBX 80 mg group, and 1 each in the FBX 120 mg and allopurinol arms); coronary artery disease (n = 3; 2 in the FBX 80 mg group and 1 in the FBX 120 mg arm), myocardial infarction (n = 2; 1 each in the FBX 80 mg and 120 mg groups), and atrial fibrillation (n = 2; 1 each in the FBX 120 mg and 240 mg arms). All of the affected subjects had underlying cardiovascular disease and/or 2 or more risk factors.

Three malignancies were recorded in the 28-week follow-up period of Study C##-009. One patient in the FBX 80 mg group developed prostate cancer on day 64. Another male patient treated with FBX 120 mg/day developed metastatic colon cancer on study day 196. A male patient who received FBX 120 mg/day was identified as having a malignant parathyroid tumour on study day 59. It was surgically resected.

One subject in the FBX 80 mg treatment group developed a severe rash (papular rash) that was considered to be probably related to FBX, and prematurely discontinued from the trial.

8.3.3.1.2. Study C##-010

Four subjects (2 subjects each in the FBX 80 mg and 120 mg groups) died during this trial, but all of the deaths were considered to be unrelated to study medication. A 77-year-old male in the FBX 80 mg arm died of retroperitoneal haemorrhage secondary to warfarin (in combination with aspirin). Another patient (65 year old male) in the FBX 80 mg group died of a combination of respiratory, heart and kidney failure on study day 61 after a 5-day septic illness. One subject (68 year old male) in the FBX 120 mg arm died from a combination of respiratory failure, anoxic encephalopathy and subsequent cardiac arrest 5 days following carotid endarterectomy surgery on study day 171. The fourth patient (74 year old male in the FBX 120 mg group) died of metastatic colon cancer.

A total of 51 subjects (including the 4 patients who died) experienced SAEs during Study C##-010. Three patients (2 FBX 120 mg and 1 allopurinol treated subject) experienced a gout flare-related SAE (that is they all resulted in hospitalization). All of the other 48 subjects who experienced SAEs (11 in the FBX 80 mg, 19 in the FBX 120 mg, and 18 in the allopurinol group) were considered to be unrelated or unlikely to be related to study medication (investigator rated). Two of the 48 subjects (1 in each FBX treatment group) recorded the SAE > 30 days after receiving their last doses of study medication, and 1 patient in the FBX 120 mg arm experienced an SAE of congestive cardiac failure on day -9 (that is before receiving their first doses of study medication). Cardiovascular events, including coronary artery disease (4 allopurinol treated patients), myocardial infarction (n = 4; 2 in the FBX 120 mg group and 1 each from the other 2 treatment arms), angina (2 patients in the FBX 80 mg group and 1 in the allopurinol arm), atrial fibrillation (1 patient in each FBX dose group) and cerebrovascular accident (1 subject in the FBX 120 mg group), were the most common type of SAE. They all occurred in subjects with pre-existing cardiovascular disease and/or risk factors for thrombotic atherosclerotic disease. Cardiovascular events occurred with similar frequency in the 3 active treatment groups (4 patients in each FBX treatment group, and 6 subjects in the allopurinol cohort).

Two patients (both in the FBX 120 mg group) developed malignancies in the 52-week follow-up period of Study C##-010. One patient developed prostate cancer on day 270. The other patient developed metastatic colon cancer on study day 273, and died of this 175 days later. No subject experienced a rash related SAE in this trial.

8.3.3.1.3. Other studies

8.3.3.1.3.1. Study F-GT##-153

Five deaths occurred in this study, 3 in patients receiving allopurinol and 1 subject in each of the FBX treatment groups. Two of the deaths (both in the allopurinol group) were considered to be due to cardiovascular events (hypertensive heart disease, and sudden death). The third death in the allopurinol group was due to adenocarcinoma of the lung, complicated by post-operative pneumonia and sepsis. In the FBX 40 mg group, a patient died due to anaphylaxis from 50 fire ant bites, and in the FBX 80 mg group a patient died due to chronic obstructive pulmonary disease and cerebral oedema. None of the deaths were judged to be study treatment related.

Overall, 2.5% of subjects (19/757) in the FBX 40 mg group, 3.7% of subjects (28/756) in the FBX 80 mg arm, and 4.1% of subjects (31/756) in the allopurinol group experienced SAE. The most frequent SAE was lower respiratory tract infection and lung infections, which were experienced by a total of 5 (0.2%) of subjects [1 subject in each FBX group, and 3 subjects in the allopurinol arm]. Other noteworthy infection related SAEs included 4 cases of cellulitis (2 allopurinol treated patients, and 1 subject in each of the FBX treatment groups), 3 cases of cholecystitis (all in allopurinol treated subjects), 3 cases of perforated appendicitis (2 cases in the FBX 40 mg group, and 1 in the FBX 80 mg arm), 2 cases of sepsis (1 each in the FNX 80 mg and allopurinol groups), and 1 case of perforated diverticulitis (allopurinol treated patient).

8.3.3.1.3.2. Study TMX-##-004

No subjects died during this short duration study. Three subjects (1 in the FBX 80 mg, and 2 in the FBX 120 mg group) experienced 5 SAEs. One subject who was treated with FBX 80 mg/day recorded 3 SAEs (pneumonia, delirium and Guillain-Barre Syndrome). The report of Guillain-Barre Syndrome was considered by the investigator to be possibly related to FBX. The episodes of pneumonia and delirium were not considered to be related to FBX. The remaining SAEs (back pain and suicide attempt) were not considered to be related to FBX.

8.3.3.1.3.3. Long-term OLE studies

A further 8 deaths were reported in the long-term OLE studies (all in subjects participating in Study C##-021): 5 male subjects receiving FBX 80 mg/day, and 3 subjects (2 male) taking FBX 120 mg/day. In total, 4 deaths (2 in each FBX dose group) were directly related to myocardial infarction. Another subject in the FBX 80 mg/day group died on study day 370 of congestive cardiac failure after suffering acute myocardial infarction complicated by heart failure on study day 13 (that is CVS related death). The other 3 deaths were related to sepsis complicating a surgical procedure (study day 337), metastatic colon cancer (study day 454) and retroperitoneal haemorrhage (female subject on study day 432 receiving concurrent warfarin and heparin). The 11 cause mortality incidence was 0.38 per 100 PY (95% CI 0.163, 0.743) in the subjects receiving FBX in the long-term OLE studies. No patients receiving allopurinol died in the long-term OLE trials.

In the long-term OLE studies, the overall number (and percentage) of FBX treated subjects who experienced a treatment-emergent SAE was 120 patients (10.5% of 1143) compared to 13 subjects (7.3% of 178) who received allopurinol therapy. When adjusted for drug exposure, the rates of SAEs per 100 PY were 9.5 for all FBX treated subjects (9.9 for FBX 80 mg and 8.0 for FBX 120 mg), and 11.3 for allopurinol therapy. As determined by the site investigator, the overall number (and percentage) of FBX treated subjects who experienced a treatment-related SAE in the OLE studies was 4 patients (0.3% of 1143) compared to zero subjects who received allopurinol therapy. When adjusted for drug exposure, the rates of treatment related SAEs was 0.3 per 100 PY for all FBX treated subjects (0.3 for FBX 80 mg and 0.2 for FBX 120 mg). In the long-term OLE studies, the pattern (that is individual type) of SAEs did not alter with prolonged drug exposure. The most commonly recorded treatment-emergent SAEs (by high level term using the MedDRA system) in the long-term OLE trials were ischaemic coronary artery disorders (1.0 per 100 PY for all FBX treated subjects, and 0.8 per 100 PY for allopurinol therapy), coronary artery disorders not elsewhere classified (0.6 per 100 PY for all FBX treated subjects, and 0.8 per 100 PY for allopurinol therapy), and lower respiratory tract and lung infections (0.6 per 100 PY for all FBX treated subjects, versus zero for allopurinol therapy).

8.3.3.1.3.4. Phase I studies

No deaths occurred in any of the Phase I trials. In all of the early phase clinical trials, only 1 subject reported an SAE in Study C##-059. This was a reported SAE of vaginal laceration, which occurred during the washout period between treatment regimens (after the subject had received a single dose of FBX 80 mg and hydrochlorothiazide 50 mg). The AE was considered unrelated to study medication by the site investigator, who reported that it had onset during sexual intercourse.

8.3.4. Discontinuation due to adverse events**8.3.4.1. Pivotal studies**

8.3.4.1.1. Study C##-009

In total, 78 subjects (7 placebo, 21 FBX 80 mg, 19 FBX 120 mg, 13 FBX 240 mg, and 18 allopurinol-treated patients experienced AEs that led to premature discontinuation from the study. None of the subjects given allopurinol 100 mg/day experienced AEs that led to withdrawal. One patient who received FBX 80 mg/day had increased hepatic enzymes on day -6

that led to premature discontinuation from the study on day 53 (that is after FBX had been started).

The most common causes of premature discontinuation from the study were diarrhoea and liver function test abnormalities. Diarrhoea occurred in all of the active treatment groups, but was more frequently recorded in the FBX groups (5 cases in the FBX 80 mg group, 1 subject in the 120 mg arm and 5 reports in the FBX 240 mg group) compared to the allopurinol arm (1 case only). Abnormal liver function tests leading to study withdrawal were observed in 3 patients treated with FBX 80 mg, 2 in the FBX 120 mg arm, and 3 in the allopurinol group (no cases in the FBX 240 mg and placebo groups).

A higher number of subjects on FBX 80 mg and 120 mg groups compared to allopurinol or placebo discontinued due to rash - 8 subjects in total (1 placebo, 3 FBX 80 mg, 3 FBX 120 mg, and 1 allopurinol patient). Most of the rashes were considered to be treatment related (6/8). All rashes were either mild or moderate in severity with the exception of 1 subject with a severe papular rash (commenced on study day 30, and continued unresolved until the last recorded follow-up 43 days later).

8.3.4.1.2. *Study C##-010*

A total of 53 patients (20 [7.8%] in the FBX 80 mg group, 25 [10.0%] in the FBX 120 mg arm and 8 [3.2%] in the allopurinol group) experienced AEs that led to premature discontinuation from the study. The most common AE related causes of withdrawal were abnormal liver function tests and skin rash, which occurred more in the FBX treatment groups compared to the allopurinol arm. The incidence of premature study discontinuation due to abnormal liver function tests was 2.0% (5/256) in the FBX 80 mg group, 2.8% (7/251) in the FBX 120 mg arm, and 0.4% (1/253) in the allopurinol group. Nine subjects (4 in each of the FBX groups, and 1 in the allopurinol set) prematurely discontinued from the study due to a skin rash that was considered to be treatment related. In terms of rash description, 5 subjects had their rash described as maculo-papular or papular; and 2 had their rash described as an exfoliative dermatitis.

8.3.4.2. *Other studies*

8.3.4.2.1. *Study F-GT##-153*

There was no statistically significant difference between the 3 treatment groups for the incidence and type of AEs that led to premature discontinuation from the trial: 6.2% (47/757) of subjects in the FBX 40 mg group, 7.8% (59/756) of patients in the FBX 80 mg arm and 8.1% (61/756) of subjects in the allopurinol group. The most frequent type of AE leading to study discontinuation was abnormal liver function tests which were experienced by 1.8% (14/757) of subjects in the FBX 40 mg group, 1.2% (9/756) of patients in the FBX 80 mg arm, and 0.9% (7/756) of subjects in the allopurinol group. Six subjects (2 in each of the 3 treatment groups) prematurely discontinued study drug due to AEs relating to acute renal failure (all but 1 of which were regarded as non-serious). Each of the 6 subjects had underlying risk factors that contributed to these events, and none of those subjects required dialysis.

8.3.4.2.2. *Study TMX##-004*

In total, 6 subjects (1 placebo, 1 FBX 40 mg, 2 FBX 80 mg and 2 FBX 120 mg patients) prematurely discontinued from the trial primarily due to AEs including diarrhoea (placebo subject on study day 3), abnormal liver function tests (FBX 40 mg patient; onset day 15 and lasted for 29 days), delirium (FBX 80 mg subject), increased serum creatinine (FBX 80 mg subject; onset day 14 and lasted for 195 days), suicide attempt (FBX 120 mg patient) and angioedema (FBX 120 mg subject; onset day 21 and lasted for 6 days). The suicide attempt and episode of delirium were considered to be not related to FBX but all other AEs leading to discontinuation were considered to have at least a possible to probable association with treatment.

8.3.4.2.3. Long-Term OLE studies

In the 2 OLE studies, the overall rates of treatment discontinuation were 15.9 per 100 PY in the FBX group (all doses combined) and 33.1 per 100 PY in the allopurinol treatment cohort. However, a higher incidence of treatment discontinuation due to AEs was observed in the FBX treated subjects (3.3 subjects per 100 PY) compared to those who received allopurinol (1.2 subjects per 100 PY). This outcome was principally due to the higher rate of abnormal investigation results, mainly abnormal liver function tests (elevated serum transaminases), in the FBX treated subjects. In addition, treatment discontinuations were greater in the FBX 80 mg/day group (almost 5.0 subjects per 100 PY) versus the FBX 120 mg/day arm (approximately 3.0 subjects per 100 PY) suggesting no FBX dose response relationship for the incidence of treatment discontinuations due to AEs.

8.3.4.2.4. Phase I studies

Among subjects who participated in the Phase I trial program, 18 of 811 (2.2%) subjects receiving FBX prematurely discontinued due to AEs occurring after the first dose of study drug and within 30 days of the final dose. Eleven of the 18 subject discontinuations were considered to be treatment-related. The most commonly reported AEs leading to premature discontinuation from FBX were hepatic (n = 6; including 5 cases of elevated serum transaminases), gastrointestinal problems such as abdominal pain and diarrhoea (n = 4), increased heart rate or ventricular extrasystoles (n = 4), rash (n = 3), increased serum creatinine (n = 2) and increased lipase or amylase (n = 2).

8.4. Laboratory tests

8.4.1. Liver function

8.4.1.1. Pivotal studies

8.4.1.1.1. Study C##-009

Liver function abnormalities in all of the Phase III studies included elevations in serum transaminases and/or bilirubin. In total, 17 subjects (5 FBX 80 mg, 5 FBX 120 mg, 1 FBX 240 mg, and 6 allopurinol 300 mg/day) had 1 or more ALT or AST values > 3x ULN at either 2 consecutive post-baseline visits or at the final study visit. Among these 17 patients, 12 (71%) had a history of social alcohol consumption and 11 (65%) had a relevant medical history (including diabetes mellitus, obesity and fatty liver disease). Three subjects in the FBX 80 mg treatment group, 2 subjects in the FBX 120 mg arm, and 3 subjects in the allopurinol treatment group prematurely discontinued from the study due to abnormal hepatic chemistry values. No subjects in the placebo, FBX 240 mg, or allopurinol 100 mg/day groups prematurely discontinued from the study because of abnormal liver function tests. Most elevations in serum transaminases resolved within 1 week of treatment cessation, and did not recur.

8.4.1.1.2. Study C##-010

In all treatment groups mean changes from baseline to week 52 in liver function tests (total bilirubin, alkaline phosphatase and transaminases) were small and not clinically relevant. A higher proportion of subjects in the FBX treatment groups (11.2% [28/250] in the FBX 80 mg, and 14.0% [34/242] in the FBX 120 mg arm) had an increase in ALT > 2x ULN during the study compared to 9.4% (23/244) of patients who received allopurinol 300 mg/day. In contrast, increases in AST > 2x ULN during the study were similar between the 3 treatment groups: 6.4% (16/250) in the FBX 80 mg, 9.1% (22/242) in the FBX 120 mg arm, and 8.2% (20/244) in the allopurinol arm. Elevations in total bilirubin of at least 2-fold were uncommon in all treatment groups affecting 3 subjects (1.2%) in the FBX 80 mg group, 9 patients (3.7%) in the FBX 120 mg arm, and 4 subjects (1.6%) in the allopurinol set.

8.4.1.1.3. Other studies

8.4.1.1.3.1. Study F-GT##-153

A total of 63 subjects experienced elevations of ALT and/or AST that were at least 3x ULN: 25 (3.3%) received FBX 40 mg/day, 20 (2.6%) received FBX 80 mg/day, and 18 (2.4%) received allopurinol. Nineteen of these subjects had both AST and ALT elevated > 3x ULN: 7 in FBX 40 mg group, 8 in FBX 80 mg arm, and 4 in the allopurinol group. No subject in the study had an ALT or AST > 3x ULN concurrent with total bilirubin > 2 mg/dL. In the group of patients with ALT or AST values > 3x ULN, a medical history of hyperlipidaemia was recorded in 13 of the 25 subjects in FBX 40 mg group compared to 8 subjects each taking FBX 80 mg or allopurinol. Of the subjects who had ALT or AST values > 3x ULN, 3 in FBX 40 mg group, and none in FBX 80 mg or allopurinol cohorts had a medical history of fatty liver. Many (46/63) of the subjects who had ALT or AST values > 3x ULN had a BMI > 30 kg/m², and most (51/63) were regular alcohol drinkers. When abnormal liver function tests were analysed by type of prophylactic gout medication, results for subjects taking colchicine were similar to those for subjects taking naproxen/lansoprazole. One subject in the allopurinol group (also receiving colchicine for prophylaxis) had a > 10x ULN for ALT and AST concurrently.

8.4.1.1.3.2. Study TMX-##-004

There were no significant differences between the treatment groups for the mean change from baseline in hepatic chemistry. However, a total of 8 male subjects in Study TMX-##-004 developed abnormal changes in hepatic chemistry during the study (that is after their last value obtained prior to commencement of prophylactic colchicine): 1 placebo patient, 2 in the FBX 40 mg group, 4 in the FBX 80 mg arm and 1 in the FBX 120 mg group. Four of the 8 subjects (1 placebo, and 3 FBX 80 mg treated patients) had elevations in AST and/or ALT values on study day 1, which the investigator considered to be due to either colchicine effect, or the subject's co-morbid disease. However, 2 of the patients experienced clinically significant abnormalities of hepatic chemistry. One subject treated with FBX 40 mg/day developed raised AST (x5 ULN) and ALT (x6 ULN) values reported as an AE on day 15, serum transaminases remained elevated on days 21 and 23, and study medication was ceased on day 22 as the investigator considered the AE to be treatment related. The AST and ALT values returned to within normal limits at the final assessment on day 43 (21 days post treatment). Another subject treated with FBX 80 mg/day developed elevated AST (x4 ULN) and ALT (x5 ULN) values reported as an AE of severe intensity on day 19, and possibly related to study medication (FBX and/or colchicine usage). At the final assessment on day 33, serum transaminases had returned to normal despite the patient continuing study treatment.

8.4.1.1.3.3. Long-term OLE studies

The incidences of patients with elevated liver function tests (mostly, mild changes) in the FBX 80 mg and 120 mg groups was slightly higher than the allopurinol treated subjects, but not statistically significant. Treatment related increases in ALT, AST or GGT were reported in 0.8%, 0.5%, and 0.2% of patients in the 40, 80, and 120 mg FBX groups (total 1.5%; 17/1143) compared with zero subjects in the allopurinol arm. This data also indicates no dose-effect relationship for the incidence of abnormal liver function tests has been observed with FBX therapy. When the data was analysed by 6-month periods up to 18 months of treatment, the incidence of abnormal liver function tests did not change with time. In the long-term OLE studies, no case of severe drug-induced liver injury was observed. However, a total of 15 subjects had either an AST or ALT $\geq 5 \times$ ULN, or an ALT and/or AST $\geq 3 \times$ ULN concurrent with total bilirubin ≥ 2.0 mg/dL. Of these 15 subjects, 6 subjects were on FBX 80 mg, 6 were on FBX 120 mg, and 3 received allopurinol. All 15 subjects had a contributing medical history (for example cholecystitis, pancreatitis, or hepatic steatosis), and/or regularly consumed alcohol, or had elevated liver function tests at baseline.

8.4.1.1.3.4. Phase I studies

In the Phase I single and multiple dose FBX studies, the proportions of subjects who developed shifts from normal to high was 6% for ALT, 4% for AST, and 1% for serum bilirubin. No more than 1% of subjects developed 2-fold increases from baseline in serum transaminases in the Phase I trials. One subject in Study TMX-##-001 developed $> \times 10$ ULN increase in serum transaminases (ALT 549 U/L and AST 1068 U/L) on day 4, which normalised at the end of the study (day 14).

8.4.2. Kidney function**8.4.2.1. Pivotal studies****8.4.2.1.1. Study C##-009**

In total, 11 subjects (2 placebo, 4 FBX 80 mg, 1 FBX 120 mg, 1 FBX 240 mg, 2 allopurinol 100 mg/day and 1 allopurinol 300 mg/day) had 1 or more serum creatinine or blood urea nitrogen (BUN) values $> 2 \times$ ULN on either 2 consecutive post-baseline visits or at the final study visit. The recorded decline in renal function was a contributory factor in 4 subjects (1 in the FBX 80 mg treatment group, 2 subjects in the FBX 120 mg arm, and 1 in the allopurinol 300 mg/day treatment group) prematurely discontinuing from the study. No clinically relevant mean changes from baseline were observed among the treatment groups for serum creatinine or electrolyte values. However, the proportion of subjects with any elevation above the ULN for BUN was numerically higher in the FBX 240 mg group (16%) compared to the placebo (6%), FBX 80 mg (7%), FBX 120 mg, and allopurinol (8%) treatment groups. The pair-wise differences of FBX 240 mg compared to placebo, FBX 80 mg, and allopurinol treatment groups were all statistically significant. However, the majority of BUN elevations were transient and resolved while continuing active treatment, or occurred in subjects with pre-existing abnormal baseline results (often reflecting some degree of renal impairment).

8.4.2.1.2. Study C##-010

In all treatment groups mean changes from baseline to week 52 in renal function tests (BUN and serum creatinine) were small and not clinically relevant. A higher proportion of subjects in the FBX treatment groups (7.6% [19/250] in the FBX 80 mg, and 8.7% [21/242] in the FBX 120 mg arm) had an increase in BUN to ≥ 31 mg/dL during the study compared to 4.9% (12/244) of patients who received allopurinol 300 mg/day. However, elevations in serum creatinine to ≥ 1.5 ULN occurred at a similar frequency in all 3 treatment groups (3-4%) during the trial.

8.4.2.1.3. Other studies**8.4.2.1.3.1. Study F-GT##-153**

A total of 1483 subjects (65.4% of 2269) had mild or moderate renal impairment at baseline in this trial. During the study, 23 of the 1483 subjects developed increases in serum creatinine levels > 1.5 mg/dL concurrent with increases in blood urea levels > 40 mg/dL: 9 subjects were in the FBX 40 mg treatment group, 5 were in the FBX 80 mg arm, and 9 were in the allopurinol group. None of the subjects who had normal renal function at baseline recorded increases in serum creatinine levels of > 1.5 mg/dL concurrent with elevated blood urea levels > 40 mg/dL during the study. All 23 subjects had a medical (that is cardiovascular) history relevant to abnormalities in renal function tests, experienced AEs during the study that were relevant to these increased laboratory values, and/or received a prior or concomitant medication that may have affected their renal function values. However, the elevations in renal function were generally mild, transient, and reversible. No subject experienced severe kidney injury or irreversible kidney damage requiring dialysis.

8.4.2.1.3.2. Study TMX-##-004

There were no significant differences between the treatment groups for the mean change from baseline in renal chemistry. Six subjects (1 in the FBX 40 mg, 2 in the FBX 80 mg and 3 in the

FBX 120 mg group) had potentially significant abnormalities in kidney function during the study. However, the majority of these abnormalities (4 patients) were considered to be either due to concurrent disease or medication, rather than FBX. However, in 2 patients the history was more complicated and their abnormalities were at least possibly related to FBX. One male subject who had mildly elevated BUN value at baseline (30 mg/dL; due to mild chronic kidney disease and hypertension) developed a further post-baseline increase in BUN on day 14 (up to 44 mg/dL), recorded as an AE, which continued for 195 days following the last scheduled study visit on day 28.

Another male subject treated with FBX 120 mg/day developed a clinically significant doubling in baseline renal function (BUN up to 39 mg/dL and serum creatinine up to 2.1 mg/dL) on day 14. The condition resolved off treatment by day 28, and was considered by the investigator to be possibly related to study medication. An alternative aetiology for the acute renal injury was considered (for example dehydration due to viral infection) but not evident.

8.4.2.1.3.3. Long-term OLE studies

In the long-term OLE studies there was no difference between the treatment groups for the incidence of abnormal renal function tests apart from a statistically higher incidence of a shift from normal to elevated BUN at some time during treatment for subjects who received FBX 80 mg/day (22.7%; 189/832) versus allopurinol 300/100 mg daily (15.2% [25/164]; $p = 0.037$). The incidence of newly raised BUN value at some point on trial was 19.6% (95/484) in the FBX 120 mg group. The frequency of raised serum creatinine (> 1.5 mg/dL, and increased from baseline by at least 0.3 mg/dL) was similar between the 3 main treatment groups: 8.5% (76/893) in the FBX 80 mg group, 5.1% (26/505) in the FBX 120 mg arm and 4.6% (8/173) in the allopurinol group. The incidence of abnormal renal function tests remained stable in the FBX treatment groups over each 6-month period up to 18 months of follow-up.

8.4.2.1.3.4. Phase I studies

No clinically significant mean or individual changes in renal chemistry were observed in the Phase I studies.

8.4.3. Other clinical chemistry

8.4.3.1. Pivotal studies

8.4.3.1.1. Study C##-009

No clinically meaningful trends were observed among the treatment groups for the mean change from baseline to the week 28 or final visit in any other clinical chemistry parameters such as magnesium, serum proteins, free thyroxine or lipids. In the pre-clinical studies involving rats (but not mice or dogs) FBX caused a decrease in free thyroxine and thyroid hyperplasia, so thyroid function tests were observed in the 2 pivotal Phase III studies.

8.4.3.1.2. Study C##-010

A statistically significant difference was observed between the FBX 120 mg and allopurinol treatment groups for the proportion of subjects who developed an abnormal post-baseline value in serum sodium (5.0% [12/242] for FBX 120 mg versus 1.6% [4/244] in the allopurinol group) and serum albumin (3.3% [8/242] for FBX 120 mg versus 0.4% [1/244] in the allopurinol group). Similarly, a statistically significant difference was observed between FBX 80 mg (9.2%; 23/249) and allopurinol (16.4%; 40/244) for the proportion of patients who developed a significant elevation post-baseline in serum triglycerides. However, these observations are likely to be sporadic and not of clinical relevance. No statistically significant differences were observed among the treatment groups for the percentage of patients who developed an abnormality from baseline to the week 52 (or final) visit in thyroid function tests. However, 1 patient (45-year-old male) treated with FBX 120 mg developed a 2-fold increase

from baseline in Thyroid Stimulating Hormone (TSH) levels on day 168, which continued until the final assessment.

8.4.3.2. Other studies

8.4.3.2.1. Study F-GT##-153

All 3 treatment groups were observed to have mean changes from baseline in several other chemistry parameters such as calcium, alkaline phosphatase, total cholesterol, and triglyceride; however all of these changes were small and not considered clinically important. Fasting laboratory measurements were not performed in this trial so lipid parameters (particularly, triglycerides) were not considered to be reliably determined.

8.4.3.2.2. Study TMX-##-004

No other significant mean or individually relevant changes in blood chemistry were observed in this study.

8.4.3.2.3. Long-term OLE studies

In the long-term OLE studies, the overall incidences of 2 non-renal chemistry parameters were higher in the FBX treatment arms versus the allopurinol group. A statistically higher proportion of patients in both the FBX 80 mg (13.9%; 111/800) and FBX 120 mg (11.1%; 52/468) developed a shift to high reading in total cholesterol during treatment compared to subjects receiving allopurinol (4.8%; 8/166). Although this finding may be explained by unequal drug exposures between the FBX and allopurinol treatment groups, it may provide a biological rationale to the higher frequency of adverse CVS events recorded in FBX treated subjects.

Abnormalities of thyroid function tests (typically, decreased free T4 and/or increased serum TSH) were more commonly observed in patients treated with FBX, raising the possibility of drug-related sub-clinical hypothyroidism. A statistically higher percentage of subjects treated with FBX 80 mg/day (4%) developed a decrease in free T4 compared to allopurinol (< 1%; p = 0.013) at some point in the long-term OLE trials. However, the incidence of TSH values above 5.5 µIU/mL was similar amongst the 3 treatment groups of interest (FBX 80 and 120 mg, and allopurinol) at 5.5%. Despite the frequency of minor abnormalities of thyroid function tests, clinically evident thyroid AEs was low in all treatment groups (1.1 subject per 100 PY for total FBX patients, and 0.6 patients per 100 PY for allopurinol). The frequency and pattern of abnormal lipid parameters and thyroid function tests did not alter with time on therapy (up to 18 months of follow-up) for the FBX treated subjects.

8.4.3.2.4. Phase I studies

Endocrinology parameters were not assessed in the single dose Phase I studies, but the multiple dose trials revealed a low percentage (< 2%) of subjects developing potentially important changes from baseline in thyroid function tests. Since XO inhibitors may cause an increase in the precursors of uric acid, xanthine and hypoxanthine, serum and urine concentrations of these precursors were collected in 3 Phase I studies. In addition, xanthine crystal urinalysis by x-ray diffraction and infrared spectroscopy was performed. Four subjects (3 received FBX 50 mg once daily, and 1 received FBX 30 mg twice daily) had 5 urine sediment samples with indeterminate results (that is very small possible traces of xanthine crystals) in 1 of the Phase I trials. In 2 of these subjects, who received a single 50 mg dose of FBX, the urinary xanthine concentration measured 6-12 hours after dosing was high at 12.9-14.2 mg/dL. In subjects with renal impairment (Study TMX-##-008), the maximum urinary xanthine concentrations following FBX 80 mg was lower in those with renal impairment (mild, moderate and severe) compared to subjects with normal renal function. It appears that subjects with renal impairment are not at a higher risk of developing xanthine calculi as a result of increased urine xanthine levels.

8.4.4. Haematology

8.4.4.1. Pivotal studies

8.4.4.1.1. Study C##-009

No clinically significant changes were observed among the treatment groups for any haematology parameter. A total of 10 subjects (3 FBX 80 mg, 1 FBX 120 mg, 1 FBX 240 mg and 5 allopurinol 300 mg/day patients) had haematology results that met the pre-defined criteria of interest. Seven of the cases had transient reductions in eosinophil count. One patient treated with FBX 80 mg/day was observed a temporary reduction in neutrophil count to 0.54 x 10³/mCL. He had a past history of this and was an ex-drinker of alcohol. Two non-drinking patients (1 in the FBX 120 mg group, and the other was treated with allopurinol) developed significant reductions (> 2g/dL) in their haemoglobin levels, which were transient.

8.4.4.1.2. Study C##-010

No clinically significant changes were observed among the treatment groups for any haematology parameter. Thirteen subjects (7 FBX 80 mg, 1 FBX 120 mg, and 5 allopurinol 300 mg/day patients) had haematology results that met the pre-defined criteria of interest. Two subjects (1 in the FBX 120 mg group, and 1 in allopurinol arm) withdrew from the study because of moderate severity thrombocytopenia (onset day 57-92). A total of 11 patients (2 in the FBX 80 mg group, 5 in the FBX 120 mg arm and 4 in the allopurinol group) developed significant reductions (≥ 2 g/dL) in their haemoglobin levels during the trial, all of which were transient and did not result in treatment discontinuation.

8.4.4.1.3. Other studies

8.4.4.1.3.1. Study F-GT##-153

All 3 treatment groups were observed to have mean changes from baseline in several other haematology parameters such as mean cell volume, total white cell count, and neutrophil count; however all of these changes were small and not considered clinically important.

8.4.4.1.3.2. Study TMX##-004

No clinically significant changes were noted in this trial. Four subjects (1 in the placebo group and 3 in the FBX 80 mg arm) developed minor changes from baseline in haematocrit values (increase or decrease) that were not clinically relevant.

8.4.4.1.3.3. Long-term OLE studies

One patient (treated with allopurinol 300 mg/day) developed an SAE of idiopathic thrombocytopenic purpura in the long-term OLE studies. The patient recorded the SAE on day 71 of allopurinol and switched to FBX 80 mg/day without return of significant thrombocytopenia. The most haematological abnormality among FBX treated subjects in the OLE trials was mild anaemia (1% in the total FBX patient cohort versus zero in the allopurinol group). The overall rate of anaemia in the OLE studies was 0.6 events per 100 PY. During the interval of follow-up between 18 and 24 months, a higher proportion of subjects treated with FBX (8% in the 80 and 120 mg dose groups) developed a shift in platelet count from normal to high compared with < 1% of allopurinol treated subjects. This observation was statistically significant for both pair-wise comparisons of FBX therapy (80 or 120 mg) versus allopurinol.

8.4.4.1.3.4. Phase I studies

The most common haematological change in the Phase I studies was a shift from normal to high readings in the reticulocyte count (10-15% across the trials). This may be explained by the frequent withdrawal of significant volumes of blood (ranging from 230-830 mL in total) for analysis during the studies. For unknown reasons, the second most common haematological change in the Phase I studies was a shift from normal to low value in prothrombin time (up to 12% incidence in the trials).

8.4.5. Electrocardiograph

8.4.5.1. Pivotal studies

8.4.5.1.1. Study C##-009

The majority of subjects had normal ECG throughout the study, or experienced ECG changes from baseline that were not considered to be clinically significant by the investigator. Seven subjects (1 placebo, 3 FBX 120 mg, and 3 allopurinol patients) recorded a change in their baseline ECG that was considered significant by the investigator. All ECGs were analysed centrally by a cardiology unit. A similar proportion of subjects in the placebo, FBX 80 mg, FBX 120 mg, FBX 240 mg and allopurinol treatment groups had at least 1 significant ECG-related event coded with the MedDRA dictionary (17%, 10%, 13%, 13%, and 13% respectively). In addition, the incidence of significant specific ECG-related events was similar across treatment groups.

8.4.5.1.2. Study C##-010

The majority of subjects had normal ECGs throughout the study or experienced ECG changes from baseline that was not considered to be clinically significant. All ECGs were analysed centrally by a cardiology unit. Nonetheless, 8 subjects (3 in the FBX 80 mg, 2 in the FBX 120 mg, and 3 in the allopurinol 300 group) developed a clinically significant post-baseline ECG change (for example heart block, atrial fibrillation or bradycardia).

8.4.5.1.3. Other studies

8.4.5.1.3.1. Study F-GT##-153

Resting ECG was performed at all study visits in this trial. The site investigator evaluated any changes from baseline in the subject's ECG as either clinically significant or not clinically significant. Subjects who experienced a CVS related AE had all their ECG tracings forwarded to a central reader for analysis. Clinically significant ECG changes were infrequent in all 3 treatment groups, apart from those recorded in the 6 subjects who experienced APTC cardiovascular events and the 26 patients who experienced non-APTC cardiovascular events.

8.4.5.1.3.2. Study TMX##-004

All ECG results at the final visit (day 28) were either unchanged from baseline or the changes were minor and not of clinical relevance; except for 1 patient in the FBX 80 mg/day group (T-wave and ST segment changes occurred between the baseline and day 28 ECG).

8.4.5.1.3.3. Long-term OLE studies

In the long-term OLE studies, the number and percentage of subjects who recorded clinically significant changes post-baseline in ECG was low in all treatment groups: zero for FBX 40 mg, 7 subjects (0.8%) for FBX 80 mg, 2 patients (0.4%) for FBX 120 mg and 3 subjects (2%) in the allopurinol group. No specific pattern of ECG changes was identified. Two subjects experienced SAEs in association with significant ECG changes in Study C##-021. One patient treated with FBX 80 mg/day suffered an acute myocardial infarction and another subject (allopurinol 300 mg/day) developed atrial fibrillation.

8.4.5.1.3.4. Phase I studies

ECGs were recorded at baseline and at various time points in 4 of the Phase I trials (Studies TMX##-001, TMX##-002, TMX##-003 and TMX##-006). In these studies, a total of 219 subjects received FBX ranging from 10-240 mg per day. No clinically significant mean changes from baseline in PR interval, QRS duration, QT interval and heart rate were observed in any of the Phase I trials. Only 1 patient developed a shift in QT_c interval from normal to prolonged (> 450 msec) in the Phase I studies, and 7 patients (3.2% of 219) were recorded to have increases from baseline in QT_c interval from normal to borderline.

8.4.6. Vital signs

8.4.6.1. Pivotal studies

8.4.6.1.1. Study C##-009

No clinically relevant differences were observed among the treatment groups for the mean change from baseline to the week 28 or final visits for any vital sign parameter (for example blood pressure). However, when paired comparisons were examined, a statistically significant difference was observed between the FBX 240 mg and allopurinol treatment groups for the mean change from baseline to the week 28 (or final) visit in systolic blood pressure. Subjects in the FBX 240 mg group experienced a mean increase in systolic blood pressure of 2.6 mmHg at week 28 and 2.1 mmHg at the final visit (baseline mean of 132.7 mmHg) compared to a mean change of -2.0 mmHg at week 28 and -1.3 mmHg at the final visit (baseline mean of 131.9 mmHg) in the allopurinol treatment group.

8.4.6.1.2. Study C##-010

No clinically significant differences were observed between the 3 treatment groups for the mean change from baseline to the week 52 (or final) visits for any vital sign parameter such as blood pressure and pulse. Very few patients ($\geq 1\%$) in any treatment group developed significant post-baseline increases or decreases in systolic or diastolic blood pressure.

8.4.6.1.3. Other studies

8.4.6.1.3.1. Study F-GT##-153

In general, vital signs were stable throughout this trial. Sporadic mean changes from baseline were observed in all treatment groups at various visits for vital signs. However, these mean changes were small and not clinically significant. No statistically significant differences were observed between treatment groups for any vital sign parameter.

8.4.6.1.3.2. Study TMX-##-004

No significant changes were identified in this short duration (4-week) study.

8.4.6.1.3.3. Long-term OLE studies

The incidence of newly diagnosed treatment-emergent hypertension was low ($< 1.2\%$) in all treatment groups in the long-term OLE studies, with no clinically significant differences between the treatment groups being observed.

8.4.6.1.3.4. Phase I studies

In the single and multiple dose Phase trials, small mean changes from baseline to the final visit were recorded in blood pressure (systolic and diastolic) and pulse rate, but none of these changes were clinically significant.

8.4.7. Cardiovascular adverse events

8.4.7.1. Pivotal studies

The proportion of subjects with investigator reported, treatment emergent primary APTC events in the 2 pivotal Phase III studies (C##-009 and C##-010) were numerically higher in the FBX 80 mg (0.8%; 4/523) and FBX 120 mg (1.0%; 5/520) groups compared to the allopurinol treated cohorts (0.2%; 1/521), but this observation did not reach statistical significance. The 95% CIs for overall primary APTC events, and each of the 4 individual types of CVS events contributing to the combined endpoint, overlapped for FBX therapy versus allopurinol treatment.

8.4.7.2. Other studies

8.4.7.2.1. Study F-GT##-153

In Study F-GT##-153, at least 1 cardiovascular AE was reported by the site investigators in 5.2% (39/757) of subjects in the FBX 40 mg group, 5.4% (41/756) of patients in the FBX 80 mg group, and 5.8% (44/756) of subjects in the allopurinol group. There was no difference between the treatments groups in any specific type of cardiovascular AE detected. The majority of treatment-emergent cardiovascular AEs were mild to moderate in severity. Pre-specified adjudication of all deaths and cardiovascular AEs identified 6 subjects experiencing an adjudicated APTC event: 3 in the FBX 80 mg group (rate 0.40; 95% CI 0.082, 1.155) and 3 in the allopurinol group (rate 0.40; 95% CI 0.082, 1.155). All subjects experiencing an adjudicated APTC event (that is non-fatal myocardial infarction [1 subject each in the FBX 80 mg and allopurinol groups], non-fatal stroke [2 patients treated with FBX 80 mg/day] or cardiovascular death [2 patients treated with allopurinol]) had prior medical histories of the condition or significant underlying risk factors (at least 2) for atherosclerotic coronary disease. In addition, a total of 26 patients suffered non-APTC cardiovascular events: 10 in the FBX 40 mg group (rate 1.32; 95% CI 0.635, 2.416), 9 in the FBX 80 mg arm (rate 1.19; 95% CI 0.546, 2.248) and 7 in the allopurinol group (rate 0.93; 95% CI 0.373, 1.898). There were not statistically significant differences in the overall rates of adjudicated non-APTC cardiovascular events between the treatment groups.

8.4.7.2.2. Long-term OLE studies

The long-term OLE trials did not show any difference in the overall incidence and type of CVS related AEs between the treatment groups (FBX and allopurinol). In addition, there was no evidence of a dose to CVS AE relationship for FBX. The overall incidence of treatment emergent cardiovascular AEs in the long-term OLE studies was 8.6% (78/910 subjects; at a rate of 6.2 per 100 PY) in the FBX 80 mg/day group, 7.3% (38/522 patients; at a rate of 6.0 per 100 PY) in the FBX 120 mg/day arm and 6.2% (11/178 subjects; at a rate of 8.3 per 100 PY) in the allopurinol treated group. In each of these treatment cohorts, the majority of the CVS AEs were cardiac in nature: 4.9% (45/910 subjects; at a rate of 3.6 per 100 PY) in the FBX 80 mg/day group, 4.6% (24/522 patients; at a rate of 3.8 per 100 PY) in the FBX 120 mg/day arm and 3.9% (7/178 subjects; at a rate of 5.3 per 100 PY) in the allopurinol treated group. The overall incidence of CVS related AEs was lower in the long-term OLE studies compared to those observed in the 2 pivotal Phase III trials (12.5 per 100 PY for FBX 80 mg, and 10.8 per 100 PY for FBX 120 mg). Furthermore, the incidence of CVS AEs did not appear to increase with every 6-month period of follow-up (up to 2 years) in the long-term studies.

Only 7 of the CVS AEs in the long-term OLE studies were considered to be treatment (FBX) related: 3 with FBX 80 mg (chest discomfort, abnormal ECG and stroke), and 4 cases with FBX 120 mg (cerebral lacunar infarct, TIA, dyspnoea and new T-wave inversion on ECG).

8.5. Post-marketing experience

The post-marketing experience includes available information as of the 8th Periodic Safety Update Report (dated June 8, 2012), which contains data with a time lock point of April 20, 2012. The estimated cumulative post-marketing exposure to FBX worldwide (21 April 2008 - 20 April 2012) is 592,238 PY, of which approximately half has occurred in the EU, 1/3 in North America and 1/6 in Asia. This estimation is based on the drug transfer data between manufacturers and wholesalers. The information will be presented according to identified and potential risks associated with FBX use.

8.5.1. Deaths

Excluding subjects involved in clinical trials, healthcare professionals have reported a total of 38 fatalities in the post-marketing phase. The SOC of cardiac disorders is the most common fatal

event, including 11 case reports of myocardial infarction. In 8 patients, the exact cause of death was not reported. In the 8th PSUR, there was a fatal case relating to liver disease in a patient taking FBX who had a history of advanced alcoholic cirrhosis.

8.5.2. Cardiovascular events

A total of 125 CVS events have been reported in 111 patients in the post-marketing experience, and 58 of these CVS events (reported by 50 patients) met the criteria for serious. The post-marketing database contains 32 cases of myocardial infarction. The majority of cases were male, with ages ranging from 35 to 91 years. More than 65% of affected patients reported either previous history of cardiovascular disease or significant risk factors for coronary atherosclerosis (for example diabetes or hyperlipidaemia). In the cases whereby latency between commencement of FBX and the onset of CVS AE was documented (23 of 32 reports), this ranged from 11 days to 9 months, with an average duration of approximately 2 months. Other types of CVS AEs included heart failure (n = 24), stroke and cerebral haemorrhage (n = 18), syncope (n = 15), venous thromboembolism (n = 12), and various types of clinically significant cardiac arrhythmias (n = 10).

8.5.3. Serious skin or hypersensitivity reactions

A total of 675 patients with 785 rash or hypersensitivity reactions have been reported in the post-marketing database over the 4 years dating from 21 April 2008 until 20 April 2012. Of these cases, 109 AEs were rated as serious (that is 13.9% of all rash/hypersensitivity cases were serious). Consistent with the overall treated population, the majority of affected patients were male. The dose of FBX therapy was reported in ~70% of cases reports, 40% of which were receiving 40 mg/day, 40% were taking 80 mg/day, 3% were receiving 120 mg/day, and the remainder were taking FBX 10-20 mg/day. The most frequent reported individual types of rash or hypersensitivity AE collected during the post-marketing surveillance were eruptions and exanthems (n = 298), pruritus (n = 96), oedema (n = 51) and urticaria (n = 37). No deaths were related to serious skin or hypersensitivity reactions, but there are reports of angioedema, anaphylactic shock, leucocytoclastic vasculitis, Stevens-Johnson Syndrome, DRESS and skin necrosis. Most of the post-marketing reports of skin reactions occurred during the first month of FBX therapy, and many of the affected patients reported previous hypersensitivity to allopurinol.

8.5.4. Hepatic effects

Cumulatively, there have been 56 serious AEs involving hepatic effects, classified as either abnormal hepatic investigations (70%) and/or hepatobiliary disorders (30%). Most of the reports relating to abnormal hepatic investigations are classified under a general terminology of increased hepatic enzyme, but the most common individual pattern of abnormal liver function tests is elevation in serum transaminases and/or accompanied by increases in serum bilirubin or GGT. The time to event onset ranges from 1 day to 1 year with no particular pattern of latency (that is abnormal liver function tests occur at a similar frequency following drug exposure for periods of up to 300 days). One case of liver disorder was associated with a fatal outcome in a patient with pre-existing advanced alcoholic cirrhosis. Another significant reported case involved a patient who developed an elevation of ALT to 4485 IU/L and AST to 6825 IU/L 38 days following commencement of FBX. The event resolved 2 days after ceasing treatment. In the post-marketing database, the dose of FBX is not routinely reported but when available does not indicate a higher incidence of abnormal liver function tests in the daily dose range of 40-120 mg.

8.5.5. Renal effects

A total of 234 cases with renal AEs are reported in the post-marketing database, 97 of which were regarded as serious (41.4% of all reports). This includes 1 fatal case with "renal failure" as the primary cause of death. The serious AEs include azotaemia, renal failure, fluid overload and tubulointerstitial nephritis. Tubulointerstitial nephritis has been proposed for addition to the

US label under immune system disorders SOC. In addition, there have been 13 cases of rhabdomyolysis, 12 of which were considered serious. Seven of the 13 cases were receiving concomitant colchicine and/or a statin drug; and 6 of the 13 patients had a history of renal disease.

8.5.6. Neurological effects

A total of 179 cases (43 rated as serious) of neurological side-effects have been reported in the post-marketing database. The serious AEs include convulsion, encephalopathy, gait disturbance, Guillain-Barre syndrome, loss of consciousness, mental disorder, altered mood, poor quality sleep, syncope and pre-syncope, psychotic behaviour and violence-related symptoms. Psychotic behaviour including aggressive thoughts has been inserted into the US label as a potential risk, but the observation is not considered to be causal.

8.5.7. Bleeding and haematological effects

A total of 91 cases with significant haematological abnormalities have been recorded in the post-marketing database. Of these, 33 patients reported 40 serious events. The haematological reports include 18 cases of thrombocytopenia (9 serious), 11 cases of pancytopenia (2 subjects received concomitant therapy with azathioprine), 10 reports of anaemia, and 2 additional cases of haemolytic anaemia.

Seven cases report bleeding (for example epistaxis, cutaneous haemorrhage and haematuria), all of which were rated as non-serious. Two of the patients were taking concurrent anticoagulant therapy. Latency ranged from 7-14 days. Cumulatively, there have also been 10 reports (5 serious) of increased INR. Oral anticoagulants were being taken by 9 of these affected patients, and 3 were also receiving concomitant colchicine as co-suspect medication.

8.5.8. Thyroid effects

Cumulatively, there have been 4 non-serious reports of increased serum TSH, and 1 non-serious report of thyroiditis (outcome unknown).

8.5.9. Drug interactions

A total of 32 potential drug interactions have been reported with FBX in the post-marketing period including 11 reports of azathioprine co-prescription resulting in significant haematological toxicity (various types of cytopenia, usually serious), 9 reports of concomitant vitamin K antagonist therapy resulting in increased INR (2 with bleeding) and 2 reports of concurrent simvastatin therapy associated with rhabdomyolysis. The remainder of the drug interaction reports are single cases of limited clinical relevance apart from 1 report. A patient taking tacrolimus following renal transplant was reported to have developed a serious increase in tacrolimus levels 2 weeks after starting FBX 40 mg/day. FBX was discontinued for 1 week and the patient's tacrolimus level returned to normal. FBX was re-introduced at a dose of 20 mg/day without recurrence of increased blood tacrolimus levels.

8.6. Safety issues with the potential for major regulatory impact

Hepatic toxicity, serious skin reactions and cardiovascular safety have been discussed earlier in this report.

8.6.1. Other safety issues

8.6.1.1. Safety in special populations

8.6.1.1.1. Use in renal impairment

In Study F-GT##-153, the rates of AEs in subjects with mild to moderate renal impairment were similar to those recorded in the overall study population. In the allopurinol treatment group of this trial, 501 subjects had mild (n = 356) or moderate (n = 145) renal impairment at baseline.

In this study, subjects with mild renal impairment received allopurinol 300 mg/day and those with moderate renal impairment received allopurinol 200 mg/day. Across treatment groups, the percentages of subjects with mild-to-moderate renal impairment who experienced at least 1 TEAE were 55.9% in the FBX 40 mg/day group, 53.7% in the FBX 80 mg/day arm and 57.7% in the allopurinol group. These event rates are similar to the overall rates of TEAEs observed in subjects with normal renal function: 57.9% in the FBX 40 mg group, 55.3% in the FBX 80 mg arm, and 56.5% in the allopurinol group. The most frequently reported individual types of AEs in patients with renal impairment were the same as those reported for all subjects. There were no overall patterns of increases or decreases in AE rates based on renal function status; however, the rates of AE due to abnormal liver function tests in subjects with normal renal function were slightly higher (9-10%) than rates in subjects with mild (6-7%) or moderate (3-6%) renal impairment across all 3 treatment groups. This difference was not considered clinically meaningful. Rates of diarrhoea were higher among subjects with moderate renal impairment receiving FBX (8-10%) compared with subjects with moderate renal impairment receiving allopurinol (7%).

In the 2 pivotal Phase III studies, the number of subjects with a history of renal insufficiency as measured by serum creatinine was too small ($n = 47$) to interpret any statistically significant comparisons between the treatment groups for AEs (incidence and type).

8.6.1.1.2. *Use in pregnancy and lactation*

One uneventful pregnancy (28 year old Caucasian) resulting in the delivery of a healthy infant at 39 weeks gestation was reported in Study TMX-##-009. The subject received 2 doses of FBX 80 mg (1 week apart) and 2 doses of FBX 20 mg (1 week apart) around the estimated date of conception.

Five male subjects receiving FBX 80 or 120 mg/day (all in Study C##-021) had partners who became pregnant while receiving active drug treatment. In the 3 of 5 pregnancies whereby the outcome was known, healthy infants were delivered.

8.6.2. **Safety related to drug-drug interactions and other interactions**

FBX drug interaction studies with azathioprine and mercaptopurine have not been performed. However, based on the mechanism of action of XO inhibition, co-administration of FBX with azathioprine or mercaptopurine is not recommended. Although the potential for inadvertent co-administration is low because these drugs are used in different populations, the potential consequences (especially, neutropenia) could be severe or life threatening. The limited post-marketing experience whereby 11 reports of co-administration of FBX and azathioprine have resulted in patient harm highlight this uncommon, but highly likely risk of significant toxicity.

Hyperuricaemia and gout frequently co-exist with CVS disorders such as atrial fibrillation, venous thromboembolism and cardiac failure, which require the use of anticoagulant drugs. In the 2 pivotal Phase III studies, warfarin was used by 7 (5.2% of 134) subjects in the placebo group, 15 (~3% of 520-523) subjects each in the FBX 80 and 120 mg groups, 2 (1.5% of 134) subjects in the FBX 240 mg arm, and 12 (2.3% of 521) subjects in the allopurinol group. While receiving warfarin, a bleeding AE was reported for 1 subject in the FBX 80 mg group (retroperitoneal haemorrhage) and 1 patient in the allopurinol group (epistaxis). A 77-year-old man in the FBX 80 mg/day group died of retroperitoneal haemorrhage. The patient did not have an increased INR around the time of the bleeding event, and was not actually taking FBX for at least 2 weeks prior to its onset. Heparin was used by 6 (~1%) subjects each in the FBX 80 and 120 mg groups, 2 (< 1%) subjects in the allopurinol arm, and no subjects in the FBX 240 mg and placebo groups. No treatment-emergent bleeding AEs were reported in subjects taking concurrent FBX and heparin.

8.7. Evaluator's overall conclusions on clinical safety

The total clinical safety dataset from the Phase I, II and III studies consists of 4072 patients in 31 studies, of which 2468 subjects were exposed to FBX 80 mg once daily and 1079 subjects were exposed to FBX 120 mg once daily, which are the requested doses in this submission. Across the Phase I, II and III studies, the duration of dosing (mean + range) in the FBX 80 mg/day treated subjects was 187 (1-1274) days and for the patients who received 120 mg/day was 201 (1-1675) days. In the long-term OLE studies (C##-021 and TMX-##-005) a total of 1143 subjects have received at least 1 dose of FBX for a mean exposure period of 850 days (representing 2661 PY of exposure), including 917 patients taking FBX 80 mg/day for a mean of 695 days (1746 PY of exposure), 524 subjects taking FBX 120 mg/day for a mean of 612 days (878 PY of exposure) and 12 patients taking FBX 40 mg/day for a mean of 1146 days (38 PY of exposure). In addition, to the clinical trial experience, there is an estimated post-marketing exposure to FBX worldwide (21 April 2008 - 20 April 2012) of 592,238 PY, of which approximately half has occurred in the EU, 1/3 in North America and 1/6 in Asia. The current safety dataset provides sufficient information about the short-term risk with FBX in the target population (such as discontinuations due to AEs, abnormalities of liver functions tests, and skin reactions), as well as potential long-term risks such as cardiovascular safety.

In general, the study populations had baseline characteristics, disease activity and concomitant medications indicative of the intended target population for the claimed indication. The majority of subjects in the Phase II and III studies were male (> 90%), Caucasian (76-87%) and middle-aged (56-59% were between the ages of 45 and 65 years). In the pivotal Phase III trials, approximately 14% of all recruited patients were aged > 65 years, but the majority of these subjects were < 75 years of age, indicating limited exposure to FBX for patients > 75 years (< 4% of all subjects). The pivotal studies included patients with common medical co-morbidities such as known atherosclerotic disease (13%), hypertension (46%), diabetes mellitus (8%) and hyperlipidaemia (33%). However, few subjects (2%) had cardiac failure at entry, which is more frequent co-morbidity in clinical practice. In addition, there is no or very limited experience in certain patient subgroups of relevance including subjects in whom the rate of urate formation is greatly increased (in particular, those with underlying malignancy), organ transplantation patients, and those with severe renal or hepatic impairment.

The key safety conclusions identified in the 3 Phase III trials are as follows:

- The overall incidence of AEs was similar in the FBX (doses ranging from 40-240 mg/day), placebo and allopurinol treatment groups.
- However, the incidence of non-infective diarrhoea was higher in patients who received FBX 240 mg/day compared with all other treatment groups (Study C##-009).
- The most frequent types of AEs in all active treatment groups (all doses of FBX, and allopurinol 100-300 mg/day) were upper respiratory tract infections, musculoskeletal pain, joint related symptoms, non-infective diarrhoea, headache, abnormal liver function tests and nausea.
- Overall treatment related AEs were similar between all active treatment groups and placebo, apart from a higher incidence of treatment related AEs being observed in the FBX 240 mg/day arm of Study C##-009, which was primarily accounted for by a greater number of diarrhoea, nausea, gastrointestinal pain and headache AEs.
- In both the FBX and allopurinol treatment groups versus placebo arm in Study C##-009, there was a numerically higher incidence of treatment related, abnormal liver function tests (2-3% for all active treatment groups versus < 1% for placebo).
- Permanent discontinuations from study medication because of AEs were similar in frequency among the active treatment groups (5-8% at 6-12 months), and the main AE

related reasons for withdrawal were diarrhoea, abnormal liver function tests and skin rashes.

- At 6-12 months of follow-up, the overall incidence of SAEs was low (< 4%; or < 0.3 per 100 PY) and similar in frequency between the active treatment groups, with the most frequent type of SAE being various types of adverse cardiovascular events.

The Phase III studies were unable to clearly identify a subset of patients at the highest risk of AEs from FBX. In particular, older patients (aged > 65 years) and those with renal impairment did not experience a higher overall rate or particular type of AEs. Study F-GT##-153 revealed a slightly higher incidence of abnormal liver function tests in those taking naproxen versus colchicine for gout flare prophylaxis (regardless of whether FBX or allopurinol was used as ULT).

In the long-term OLE studies, the incidence of treatment emergent and treatment related AEs (overall, and for each type of frequent or special interest AE) was lower compared to the controlled trial experience. In the Phase II, dose-finding study (TMX-##-004) of 28 days duration, patients who received FBX (40-120 mg/day) versus placebo experienced more diarrhoea and abnormalities of liver function tests.

There is an association between patients with hyperuricaemia and gout, and a greater risk of cardiovascular disease. Study F-GT##-153 specifically examined the rate of adverse cardiovascular outcomes over 6 months of follow-up in patients receiving FBX 40 or 80 mg/day versus allopurinol, as the 2 preceding Phase III studies (C##-009 and C##-010) observed a higher incidence of CVS related AEs in the FBX treatment groups compared to allopurinol and placebo. In particular, the proportion of subjects with primary APTC events in the 2 pivotal Phase III studies (C##-009 and C##-010) were numerically higher in the FBX 80 mg (0.8%; 4/523) and FBX 120 mg (1.0%; 5/520) groups compared to the allopurinol treated cohorts (0.2%; 1/521), but this observation did not reach statistical significance. In Study F-GT##-153, at least 1 cardiovascular AE was reported by the site investigators in 5.2% (39/757) of subjects in the FBX 40 mg group, 5.4% (41/756) of patients in the FBX 80 mg group, and 5.8% (44/756) of subjects in the allopurinol group. There was no difference between the treatments groups in any specific type of cardiovascular AE detected. Pre-specified adjudication of all deaths and cardiovascular AEs identified 6 subjects experiencing an adjudicated APTC event: 3 in the FBX 80 mg group (rate 0.40; 95% CI 0.082, 1.155) and 3 in the allopurinol group (rate 0.40; 95% CI 0.082, 1.155). In addition, a total of 26 patients suffered non-APTC cardiovascular events: 10 in the FBX 40 mg group (rate 1.32; 95% CI 0.635, 2.416), 9 in the FBX 80 mg arm (rate 1.19; 95% CI 0.546, 2.248) and 7 in the allopurinol group (rate 0.93; 95% CI 0.373, 1.898). No statistically significant difference in the overall rates of adjudicated non-APTC cardiovascular events between the treatment groups was concluded.

Death has been reported in 14 subjects exposed to FBX (8 receiving 80 mg/day, 5 taking 120 mg/day and 1 receiving 40 mg/day) in the Phase III and long-term OLE studies (6 patients in the controlled trials, and 8 in OLE studies). At least 4 of the deaths were related to myocardial infarction and another 2 suffered cardiac failure. In the post-marketing, a total of 38 deaths have been recorded, 11 of which are attributable to myocardial infarction. However, the mortality rates and types of deaths observed in the clinical studies and post-marketing database is consistent with those expected in the target population. A total of 6 malignancies were recorded in the 3 Phase III studies, and there were a few deaths related to sepsis. Again, this result is within expectations for the target population.

Rash and hypersensitivity reactions are an AE of special interest in drugs with an effect on XO (FBX and allopurinol). In Study C##-009, the incidence of rash AEs was similar in the placebo (2%), all FBX treatment groups (2-3%) and allopurinol treatment groups (2%). However, in Study C##-010 7.6-10.9% of subjects in all 3 treatment groups (FBX 80 and 120 mg/day, and allopurinol) reported at least 1 rash AE. In Study TMX-##-004, 8.7% (10/115) of subjects treated with FBX developed rash or allergy related AEs, including 1 subject who experienced

angioedema of the upper lip and prematurely discontinued from the study. Overall, the majority of rash AEs observed in the clinical trials resolve while continuing treatment, and were graded as either mild or moderate in severity. The risk of skin or hypersensitivity reaction does not appear to be related to FBX dose. No deaths related to serious skin or hypersensitivity reactions have been reported in either the clinical trials or post-marketing database, but there are reports of serious and major reactions (such as angioedema, Stevens-Johnson Syndrome, and skin necrosis). Most of the post-marketing reports of skin reactions occurred during the first month of FBX therapy, and many of the affected patients reported previous hypersensitivity to allopurinol indicating a general predisposition to allergic reactions.

In the 3 Phase III studies, a higher frequency of abnormal liver function tests (mainly, elevated serum transaminases and/or minor increases in bilirubin) was observed in all of the active treatment groups (3-5% in FBX and allopurinol treatment groups) versus placebo (< 1%). The incidence of abnormal liver function tests did not increase with time in the long-term trials. Study F-GT##-153 suggested that when NSAID was used for gout flare prophylaxis (versus colchicine) there was a slightly higher incidence of abnormal liver function tests. The majority of patients who developed elevations in liver function tests were regular consumers of alcohol, had BMI > 30 kg/m² or had additional hepatic risk factors (such as pre-existing hepatic steatosis). Nonetheless, there have been post-marketing reports of severe hepatic reactions in association with FBX therapy, including fatality. The risk of abnormal liver function tests is not related to FBX dose.

The safety dataset also reveals a low incidence of renal and haematological (including bleeding) AEs. Although the pre-clinical studies raised the possibility of abnormalities of thyroid function, the clinical trial dataset did not reveal any significant pattern of thyroid dysfunction in association with FBX use in humans. When FBX is administered at doses of 40-240 mg/day, no clinically relevant effects upon resting 12-lead ECGs and vital signs is observed. As demonstrated in the post-marketing experience there is a low but serious risk of major toxicity (haematological) when FBX is co-prescribed with azathioprine.

In summary, the safety data indicates that FBX has an acceptable and comparable safety profile to the current standard of care (allopurinol) in patients with hyperuricaemia and gout. There are some significant associated safety concerns including the risk of liver function test abnormalities, skin and hypersensitivity reactions, and major adverse cardiovascular events. If approval were granted for FBX in the management of hyperuricaemia in patients with gout, ongoing pharmacovigilance for the above types of AEs (as well as all cause mortality, renal effects and potential drug interactions) would be advised.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of FBX in the proposed usage are:

- Higher proportion of subjects treated with FBX 80 and 120 mg/day achieving a desirable target serum urate level of < 6.0 mg/dL after 26-52 weeks of treatment compared to placebo and allopurinol.
- Study F-GT##-153 demonstrates that FBX 80 mg/day is more efficacious than dose-adjusted allopurinol in lowering serum urate levels to < 6.0 mg/dL in those with mild or moderate renal impairment.
- Long-term, open-label studies (TMX-##-005 and C##-021) support the maintenance of treatment effect with FBX for up to 5 years of therapy.

- Availability of an alternative urate lowering therapy in a patient group that is relatively common and with an unmet need for additional effective therapies.

9.2. First round assessment of risks

The risks of FBX in the proposed usage are:

- Risk of non-infective diarrhoea, headache and nausea
- Possible increased rate of thromboembolic cardiovascular events (versus allopurinol in the 2 pivotal Phase III studies, but similar in a 3rd and subsequent Phase III study),
- Increased risk of skin and hypersensitivity reactions (versus placebo; but similar incidence to allopurinol),
- Increased risk of abnormal liver function tests (versus placebo; but similar incidence to allopurinol).
- Potential for serious drug interaction if co-prescribed with azathioprine, and increased INR vigilance when added to vitamin K antagonist treatment,
- Risk of gout flares, particularly during the initiation of therapy, and the need for the co-prescription of gout prophylaxis treatment (either NSAID or colchicine) for 6 months after the initiation of FBX, and
- Insufficient information in certain patient subgroups such as those who have high rates of urate production, organ transplantation and patients with severe renal or hepatic impairment.

9.3. First round assessment of benefit-risk balance

The overall benefit-risk balance of FBX, given the proposed usage, is favourable. The current submission has provided robust evidence that FBX therapy in patients with hyperuricaemia and gout results in a clinically meaningful effect in the appropriate disease related outcomes (for example significant lowering of serum urate levels) at an acceptable risk profile (short and long-term). There is a substantial unmet need for additional urate lowering drug therapies in patients with hyperuricaemia and gout. The benefits of FBX therapy for the claimed indication are statistically significant, and also of clinical relevance and magnitude. The current dataset for use of FBX in patients with hyperuricaemia and gout is extensive and has been replicated in several well-conducted clinical studies in the target population. There are some significant potential risks associated with FBX therapy, including abnormal liver function tests, a possible association with major adverse cardiac events, and severe skin and hypersensitivity reactions. The population assessed in the Phase II-III study program had external validity to the needed patient groups in Australian clinical practice. On balance, the known and potential benefits of FBX therapy outweigh the currently identified risks when used appropriately in the target population.

10. First round recommendation regarding authorisation

This evaluator would recommend acceptance of the sponsor's proposed registration of FBX for the indication of treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (gouty arthritis and/or tophus formation). Consistent with the approved EU posology, I would recommend the sponsor proposed dose of FBX to be 80 mg taken once daily, with or without food. If the serum uric acid is > 6 mg/dL (357 µmol/L) after 2-4 weeks, FBX 120 mg once daily may be considered. No dose adjustment is recommended in patients with mild or

moderate renal insufficiency, mild hepatic impairment or in the elderly. Gout flare prophylaxis of at least 6 months is recommended.

11. Clinical questions

11.1. Pharmacokinetics

Question One: Could the sponsor provide information demonstrating that the proposed commercial presentation of febuxostat has been optimally formulated? In particular, has the bioavailability of the proposed febuxostat formulation been compared relative to an oral solution? This is a TGA recommendation for licensing of new immediate release oral dose forms.

Question Two: Could the sponsor provide the final study report with results of Study TMX-##-103, which was a Phase I crossover trial, which examined the effect of multiple doses of febuxostat on the pharmacokinetics of a single oral dose of rosiglitazone and its metabolite? Only the protocol of Study TMX-##-103 was provided.

11.2. Pharmacodynamics

Question Three: Could the sponsor elaborate on the possible reasons for moderate inter-individual variability for the relationship between the concentration of febuxostat at steady state and 50% decrease in serum urate concentrations from baseline?

Question Four: Could the sponsor provide information and comment on whether it is anticipated that febuxostat may have a potential pharmacodynamic interaction (increased bleeding risk) with new oral anticoagulants, in particular rivaroxaban, dabigatran and apixaban?

11.3. Efficacy

Nil.

11.4. Safety

Question Five: In Study F-GT##-153, concomitant clopidogrel therapy was an exclusion criterion at baseline. Could the sponsor clarify if anti-platelet drugs (other than low dose aspirin) were an exclusion criterion for the 2 other Phase III Studies (C##-009 and C##-010)? In addition, does the exclusion of patients taking concurrent clopidogrel limit the external validity of the study's findings?

12. Second round evaluation of clinical data submitted in response to questions

The sponsor's response dated 27 September 2013 addresses 6 questions that were raised in the first round clinical assessment. Each of these responses will be assessed in order.

Question One: The sponsor states that an absolute bioavailability study for FBX is not justified because the development of an oral FBX solution is not feasible for 3 reasons: low FBX solubility, unfavourable organoleptic properties, and the potential for mucosal irritation and damage. In addition, the sponsor asserts that the current submission articulates the dissolution profile of the medicine, and bioequivalence studies support the optimal formulation of the proposed commercial presentation of FBX. I concur with the sponsor opinion that justification for not performing an absolute bioavailability study has been presented.

Question Two: The sponsor has provided the final report for Study TMX-##-103, and included the pertinent information (that is no evidence of a significant interaction between FBX and rosiglitazone/CYP2C8 substrates) in the proposed PI (page 10 – “Interactions with Other Medicines” section).

Study TMX-##-103 was a Phase I, double-blind, randomized, 2-period cross-over trial conducted at a single site in USA which examined the effect of multiple doses of FBX (120 mg daily for 9 consecutive days) on the PK of a single 4 mg oral dose of rosiglitazone (taken on day 5) and its metabolite, N-desmethylrosiglitazone. The rationale for this trial was that preclinical studies showed that FBX was a weak inhibitor of CYP2C8 in vitro. Rosiglitazone is predominately metabolized by CYP2C8, with CYP2C9 contributing as a minor pathway. Therefore, rosiglitazone and its major active metabolite, N-desmethylrosiglitazone were considered to be suitable agents to assess the impact of FBX on CYP2C8 in human subjects.

The study recruited a total of 39 otherwise healthy patients (27 male and 12 female) between the ages of 22 and 52 years (mean age 34.4 years). The majority of recruited subjects were Caucasian (84.6%; 33/39), and the remainder of subjects (15.4%; 6/39) were of African American racial background. It was conducted between November 2009 and January 2010 at a single study centre in the USA. In total, 36 subjects completed both 10-day study periods of confinement. Two of the patients who prematurely discontinued withdrew because of AEs (newly identified CrCL < 90 mL/min, and elevated serum transaminases, on admission for study period 2).

Study TMX-##-103 showed that the exposure (Cmax and AUC) of rosiglitazone and its metabolite N-desmethylrosiglitazone were comparable across the 2 regimens (FBX 80 mg versus matching placebo tablets). The mean Cmax and AUC values for rosiglitazone following FBX were 308.6 ng/mL and 1594 ng.hr/mL, respectively, compared with 327.6 ng/mL and 1564.5 ng.hr/mL, respectively, following placebo. In addition, the mean CL (2.6 L/hr) and T1/2 (4.1 hours) of rosiglitazone was identical after the co-administration of FBX compared to placebo. The mean PK values for Cmax (82 ng/mL), AUC (2495 ng.hr/mL) and T1/2 (8.1 hours) for N-desmethylrosiglitazone were also comparable between FBX 80 mg and placebo regimens.

Overall, the results of Study TMX-##-103 indicate that co-administration of FBX and rosiglitazone has no effects on the PK of rosiglitazone and its metabolite, N-desmethylrosiglitazone. In addition, this study provides information that FBX does not appear to alter in vivo CYP2C8 activity.

Question Three: The sponsor states that data from 2 population PK-PD studies (TMX-##-005 and C##-009) was used in examining covariate effects on the PD parameter of IC50 (that is FBX concentration resulting in 50% decrease in serum urate). No specific factor was identified as being correlated with IC50 response and the question remains unanswered. I would not regard the lack of information on this issue as being a barrier to licensing. In clinical practice, individual patients would have their serum urate concentrations monitored while receiving FBX, and dose adjustments could be made depending on individual response to therapy.

Question Four: The sponsor states there is no potential PD interaction between FBX and coagulation factors. Furthermore, there are no anticipated PK interactions between FBX and oral anticoagulant medicines based on the known major metabolic pathways of the drugs. I concur with the sponsor opinion but recommend post-marketing pharmacovigilance of this potential issue if registration in Australia is granted.

Question Five: In Study F-GT##-153, concomitant clopidogrel therapy was an exclusion criterion at baseline. Could the sponsor clarify if anti-platelet drugs (other than low dose aspirin) were an exclusion criterion for the 2 other Phase III Studies (C##-009 and C##-010)? In addition, does the exclusion of patients taking concurrent clopidogrel limit the external validity of the study's findings?

The sponsor states that in Study F-GT##-153 patients taking clopidogrel were not specifically excluded, however, protocol amendment 2 stated that subjects receiving concurrent clopidogrel and naproxen were prohibited because of an increased risk of occult gastrointestinal blood loss. Studies C##-009 and C##-010 required either naproxen or colchicine to be used as gout flare prophylaxis. No specific mention of concurrent clopidogrel therapy was mentioned in those study's protocols. After clarifying the above details, I concur with the sponsor that the external validity of Study F-GT##-153 was not significantly compromised by the exclusion of patients taking concurrent clopidogrel and naproxen as this would be recommended contemporary clinical practice in Australia.

Question Six: PI negotiations are beyond the scope of this AusPAR.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

No new clinical information regarding efficacy and benefits was requested by the evaluator or provided by the sponsor in the second round evaluation. Accordingly, the benefits of FBX are unchanged from those identified in the first round.

13.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of FBX in the proposed usage are unchanged from those identified in the first round.

13.3. Second round assessment of benefit-risk balance

The benefit-risk balance of FBX, given the proposed usage, is favourable.

14. Second round recommendation regarding authorisation

This evaluator would recommend acceptance of the sponsor's proposed registration of FBX for the indication of treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (gouty arthritis and/or tophus formation). This evaluator would also recommend acceptance of the sponsor proposed posology of FBX 80 mg daily (with or without food), and if the serum uric acid remains > 6 mg/dL (357 μ mol/L) after 2-4 weeks of therapy, then the daily dose of FBX may be increased to 120 mg. In addition, gout flare prophylaxis for at least 6 months is recommended.

15. References

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