Febuxostat in the treatment of gout: 5-yr findings of the FOCUS efficacy and safety study

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Objectives. This 5-yr study assessed urate-lowering and clinical efficacy and safety of long-term febuxostat therapy in subjects with gout. The primary efficacy end-point was reduction to and maintenance of serum urate (sUA) levels < 6.0 mg/dl.

Methods. Subjects who completed a previous 28-day study were entered into an open-label extension study and initially received febuxostat 80 mg daily. Between Weeks 4 and 24, dosing could be adjusted to febuxostat 40 or 120 mg. All subjects received gout flare prophylaxis during the first 4 weeks. Gout flares were recorded and treated throughout the study, and sUA, baseline tophi and safety were monitored.

Results. Among 116 subjects initially enrolled, dose adjustments were made for 44 (38%) subjects. As a result, 8 subjects received febuxostat 40 mg, 79 received 80 mg, and 29 received 120 mg daily maintenance dose. At 5 yrs, 93% (54/58) of the remaining subjects had sUA < 6.0 mg/dl. Fifty-eight subjects (50%) discontinued prematurely; 38 did so in the first year. Thirteen subjects withdrew due to an adverse event. Sustained reduction of sUA was associated with nearly complete elimination of gout flares. In 26 subjects with a tophus at baseline, resolution was achieved in 69% (18/26) by last visit on study drug at any point during the study (Final Visit). There were no deaths reported during the study.

Conclusions. Long-term treatment with febuxostat resulted in durable maintenance of sUA < 6.0 mg/dl for most subjects. There was nearly complete abolition of gout flares in patients completing the study. Baseline tophi resolved in a majority of subjects.

Key words: Febuxostat, Gout, Hyperuricaemia, Allopurinol.

Introduction

Hyperuricaemia, defined as serum urate (sUA) concentration exceeding the solubility of urate in extracellular fluid (~6.8 mg/dl), predisposes affected individuals to urate crystal formation and deposition [1, 2] as well as the clinical features of gout [1–3]. Increasing levels of hyperuricaemia increase the risk for the occurrence of gouty arthritis [3] and uric acid urolithiasis [4]. Untreated, gout may progress to a chronic disease characterized by destructive arthropathy and deposit formation of urate crystals (tophi).

The primary goal in management of gout is reduction to and maintenance of sUA in a sub-saturating range (usually < 6.0 mg/dl); it is believed that long-term achievement of this objective results in a decreased incidence or disappearance of gout flares and dissolution of tophaceous deposits [3, 5–9]. The two pharmacological methods currently employed for urate lowering in gout are reduction of urate production by use of the xanthine oxidase (XO) inhibitor, allopurinol, and enhancement of urinary uric acid excretion with a uricosuric agent. A third urate-lowering strategy, conversion of uric acid to allantoin by administration of a modified or unmodified recombinant uricase, is in development for treatment of gout refractory to currently available urate-lowering agents [10, 11].

Febuxostat is an orally administered selective inhibitor of XO [12–16] in development for the treatment of hyperuricaemia in patients with gout. The drug has potent hypouricaemic and hypouricosuric properties [12, 13, 16] but is not a purine analogue. Febuxostat is primarily metabolized in the liver to inactive acylglucuronide metabolites and, to a minor extent, by cytochrome P450 enzymes to active oxidized metabolites [14]. Although ~ 50% of the administered febuxostat is excreted in the urine, only ~10% is as unchanged drug or active metabolites [17].

Results of three double-blind studies of the safety and efficacy of febuxostat in subjects with gout and sUA > 8.0 mg/dl have previously been reported: a 28-day Phase 2, placebo-controlled trial [5]; a 28-week Phase 3 trial comparing febuxostat with allopurinol and placebo [18]; and a 52-week Phase 3 febuxostat and placebo comparative trial [19]. In all three studies, febuxostat produced significant dose-dependent decreases in sUA. Here, we present the results of a 5-yr open-label extension of the 28-day Phase 2 trial (FOCUS: Febuxostat Open-label Clinical trial of Urate-lowering efficacy and Safety). Our objectives were to evaluate the durability of febuxostat urate-lowering and the clinical efficacy, safety, and tolerability of febuxostat-induced sUA reduction and maintenance at sub-saturating levels. Clinical efficacy was assessed by changes in the incidence of acute gout flares that required treatment and by resolution of tophi that were palpable at baseline.

Subjects and methods

Study design and procedures

This open-label extension study was conducted at 23 centres in the United States. Institutional review board approval was obtained, and all subjects provided written informed consent and Health Insurance Portability and Accountability Act authorization prior (as of April 2003) to any study-related procedure. Data from last visit on study drug at any point during the study (Final Visit) (Day 28) in the preceding double-blind study were considered Day 1 data for the extension study [5]. Baseline sUA was defined as the value obtained 2 days prior to the start of the 28-day double-blind study period. The uric acid production status of each subject, roughly defined as overproducer (> 800 mg/day) or underexcreter (≤ 500 mg/day), was determined at the time of the initiation of the 28-day Phase 2 study by measurement of 24-h urinary uric acid excretion.

Inclusion criteria included enrolment and completion of the 28-day Phase 2 study [5]. Subjects with mild or moderate renal impairment, defined for this study as serum creatinine of > 1.5 mg/dl or creatinine clearance of > 50 to ≤ 80 ml/min were included in this extension study. All female subjects had to be...
surgically sterile, using acceptable means of contraception or post-menopausal to be eligible. Females who were nursing or pregnant were not enrolled. Additional inclusion and exclusion criteria were as previously described [5]; subjects consuming more than 14 alcoholic drinks/week were excluded. There was no restriction on purine intake.

Of 145 subjects completing the 28-day Phase 2 trial, 116 enrolled in the extension study. Each subject initially received febuxostat 80 mg daily for 4 weeks. In the period between Weeks 4 and 24, the dose of febuxostat could be titrated among doses of 40, 80 or 120 mg daily in order to maintain sUA between 3.0 and <6.0 mg/dl, to respond to an adverse event (AE), or at the discretion of the investigator. Dose adjustments could be made up to three times at study visits between Weeks 4 and 24. By Week 28, subjects were required to have been receiving a stable dose for at least 4 weeks. All subjects were provided with colchicine prophylaxis (0.6 mg twice daily) for the first 4 weeks of this open-label study.

Study visits occurred at Weeks 2 and 4, and then every 4 weeks through Week 56. Visits during Years 2–5 occurred every 8 weeks, except for the end-of-each-year visit, which was 4 weeks after the previous visit (i.e. Week 204 and then Week 208). Assessments at each visit included efficacy (sUA) and safety. Safety was monitored by the assessment of AEs and concomitant medication, laboratory tests, physical examination and vital signs. Investigators estimated the severity of reported AEs (mild, moderate or severe) and their potential relationship to the study drug (related or not related).

At each visit, gout flares experienced since the prior visit were recorded. Gout flares were treated at the investigators’ discretion, both during and after the prophylaxis period. Recommended gout flare medications included colchicine, NSAIDS, analgesics (i.e. acetaminophen) and corticosteroids. Only treated flares were ultimately recorded as flares. Assessments of baseline index tophi were performed at Weeks 52, 104, 156, 208 and 260, and at Final Visit.

Study end-points

Efficacy analyses were carried out on all subjects who received at least one dose of febuxostat on or after Day 1 of this open-label extension study. The primary efficacy end-point was the proportion of subjects that achieved and maintained sUA <6.0 mg/dl. The secondary efficacy end-point was the percent reduction from baseline sUA. Additional efficacy endpoints included the proportion of subjects with sUA <5.0 and <4.0 mg/dl, the proportion of subjects requiring treatment for gout flare and the resolution of palpable tophi.

Study analyses and evaluations

Study data were obtained between 21 March 2001 and 29 December 2006. All subjects who received at least one dose of study drug were included in the efficacy and safety analyses. Baseline data were obtained prior to treatment in the previous study.

The number and percentage of subjects that achieved the primary efficacy end-point, sUA <6.0 mg/dl, at Weeks 28, 52, 80, 104, 156, 208 and 260 were summarized. Summary statistics were also generated at each study visit for secondary efficacy end-points.

Analysis of the primary and secondary efficacy end-points included stratification by baseline sUA, renal function [normal or impaired (defined as serum creatinine >1.5 mg/dl or calculated creatinine clearance ≤80 ml/min)], uric acid production (underexcretion vs overproduction), age, gender, race, BMI at baseline, tophi present at baseline and history of kidney stones.

The number and percentage of subjects with treatment-emergent AEs were summarized by system and proposed relationship to the study drug.

All statistical tests were two-sided at the 0.05 significance level. Computations were performed prior to rounding, and statistical significance was determined by using P-values rounded to three decimal places. Efficacy and safety variables were analysed by final stable dose and/or by dose at observation. Final stable dose reflects the maintenance dose a subject received after dose changes were no longer allowed. For analyses by dose at observation, subjects were summarized by the dose they received at the time of the observation, and the denominator for a dose included all subjects exposed to the dose for the time interval summarized. Subjects whose febuxostat doses were titrated between Weeks 4 and 24, and thus received more than one dose, may be summarized in more than one dose group.

Results

Baseline characteristics and concomitant medication use

The majority of subjects were Caucasian (85%; 99/116) and male (91%; 105/116). The mean age of the subjects at entry was 53.3 yrs. Tophi were identified at baseline in 22% (26/116) of the subjects. Impaired renal function was defined in this study as serum creatinine >1.5 mg/dl or creatinine clearance ≤80 ml/min, and was identified in 59% (68/116) of the subjects. Mean sUA at baseline (determined at the time of enrolment into the initial 4-week Phase 2 double-blind study) was 9.70 mg/dl, 35% of the subjects (41/116) had baseline sUA ≥10 mg/dl and 76% (88/116) were hyperuricaemic due to underexcretion of uric acid (Table 1). The mean body weight of the study population was 104.5 kg (230.4 lbs), and mean BMI was 32.9 kg/m². The most common comorbid conditions were obesity (BMI >30 kg/m²; 67%; 78/116), hypertension (52%; 60/116), hyperlipidaemia (46%; 53/116) and cardiovascular disease (23%; 27/116).

During the study, 98% (114/116) of the subjects used medications other than febuxostat and colchicine (for Table 1. Summary of baseline characteristics of the study population

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>All subjects N = 116</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td>Male 105 (91)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>Caucasian 99 (85)</td>
</tr>
<tr>
<td></td>
<td>Black 9 (8)</td>
</tr>
<tr>
<td></td>
<td>Hispanic 3 (3)</td>
</tr>
<tr>
<td></td>
<td>Asian 2 (2)</td>
</tr>
<tr>
<td></td>
<td>Other 3 (3)</td>
</tr>
<tr>
<td>Age, yrs (mean (SD))</td>
<td>53.3 (12.7)</td>
</tr>
<tr>
<td>Range</td>
<td>23–78</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>Mean (SD) 32.9 (5.7)</td>
</tr>
<tr>
<td>Range</td>
<td>23–49</td>
</tr>
<tr>
<td>≥30, n (%)</td>
<td>78 (67)</td>
</tr>
<tr>
<td>Comorbidity history, n (%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>60 (52)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>53 (46)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>27 (23)</td>
</tr>
<tr>
<td>Tophi, n (%)</td>
<td>Present 26 (22)</td>
</tr>
<tr>
<td>sUA, mg/dl</td>
<td>Mean (SD) 9.7 (1.30)</td>
</tr>
<tr>
<td>Range</td>
<td>7.7–16.1</td>
</tr>
<tr>
<td>Uric acid production, n (%)</td>
<td></td>
</tr>
<tr>
<td>Underexcretors</td>
<td>88 (76)</td>
</tr>
<tr>
<td>Overproducers</td>
<td>26 (22)</td>
</tr>
<tr>
<td>Missing</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Renal function, n (%)</td>
<td>Impaired 68 (59)</td>
</tr>
</tbody>
</table>

All baseline characteristics from entry into 28-day study. aComorbidity history as self-reported by subjects at enrolment. bSerum creatinine >1.5 mg/dl or creatinine clearance ≤80 ml/min.
prophylaxis). The most common concomitant medications used were anti-inflammatory and analgesic drugs. In addition, anti-hypertension agents, including diuretics and anti-hyperlipidaemic drugs, were frequently used as ongoing treatment for the common comorbid conditions of hypertension and hyperlipidaemia.

**Subject disposition**

In the majority of subjects (62%; 72/116), no change from the initial febuxostat dose of 80 mg/day was made. Among 44 subjects receiving dose adjustment, a single change in dose was made in 32 subjects: a reduction from 80 to 40 mg in 4 subjects, and an increase from 80 to 120 mg in 28 subjects. Eleven subjects had two adjustments: from 80 to 40 to 80 mg in three subjects; from 80 to 120 to 40 mg in four subjects; and from 80 to 120 to 80 mg in four subjects. Multiple dose adjustments were made in one subject: from 80 to 120 to 80 to 40 to 120 mg; this was a deviation from protocol, as the subject exceeded the allotted number of titrations. Distribution of subjects by final stable dose and premature discontinuation patterns are provided in Fig. 1.

Fifty-nine of the subjects initially enrolled completed at least 5 yrs (260 weeks) of the trial. Fifty-eight subjects (50%) terminated prematurely, 22 (19%) subjects were terminated due to ‘personal reasons’ (not further characterized) and 13 (11.2%) subjects withdrew because of an AE. Nine subjects withdrew for ‘other reasons,’ eight because of gout flares and five because of failure to follow-up. One subject was discontinued for a protocol violation (enrolment in another clinical trial). Fifty-eight subjects withdrew during the 5-yr study, with 38 withdrawing in the first year.

**Efficacy**

The primary end-point was the proportion of subjects with sUA <6.0 mg/dl. At Week 260, 93% (54/58) of all subjects who remained in the study had sUA <6.0 mg/dl. Overall, sUA at Final Visit was <6.0 mg/dl in 83% of all subjects (95/114; two subjects did not have qualifying post-baseline sUA). The percent of subjects in each febuxostat dose group that achieved sUA <6.0 mg/dl at selected study visits is shown in Table 2.

The secondary efficacy end-point was the percent reduction from baseline sUA at each study visit. Among all subjects, mean percent sUA reductions from baseline ranged from 45 to 59% across all visits. Across doses, the percent reductions in sUA were

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**Completed 28-day double-blind study**

n = 145

**Enrolled in FOCUS trial and received febuxostat 80 mg daily**

n = 116

**Final Stable Dose, Week 24**

- 40 mg daily
  - n = 8
- 80 mg daily
  - n = 79
- 120 mg daily
  - n = 29

**Premature Discontinuation, n = 58**

- Year 1: 38 (32.8%)
- Year 2: 7 (6.0%)
- Year 3: 5 (4.3%)
- Year 4: 6 (5.2%)
- ≥Year 5: 2 (1.7%)

**Primary Reason for Discontinuation**

- Personal Reasons: 22 (19.0%)
- Adverse Event: 13 (11.2%)
- Other: 9 (7.8%)
- Gout Flare: 8 (6.9%)
- Lost to Follow-up: 5 (4.3%)
- Protocol Violation: 1 (<1%)

**Completed Study**

- 40 mg daily
  - n = 6
- 80 mg daily
  - n = 41
- 120 mg daily
  - n = 11

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**FIG. 1. Subject disposition.**
similar at Final Visit, with percent reductions from baseline of 49.2, 47.1 and 50.7% for febuxostat doses of 40, 80 and 120 mg, respectively.

Across visits, the proportions of all subjects achieving sUA <5.0 or <4.0 mg/dl were 47–66 and 11–28%, respectively.

Overall, 47% (55/116) of all subjects reported gout flares that required treatment while on their maintenance dose. The percentage of subjects that received treatment for gout flares throughout the study, by maintenance dose, was 75% (6/8) of those taking febuxostat 40 mg; 47% (37/79) of those taking febuxostat 80 mg; and 41% (12/29) of those taking febuxostat 120 mg. However, over time, the percentage of subjects that required treatment for gout flares declined to zero during the fifth year of treatment (Fig. 2).

The incidence (at 6-month intervals) of gout flares in subjects with and without tophi differed. After 12 months of treatment on the maintenance dose, <10% of the subjects without baseline tophi reported gout flares compared with as high as 31% of the subjects with baseline tophi. Within the latter group, the percent of subjects that reported flares decreased to <10% after Month 48.

Among the 26 subjects with a palpable tophus at baseline, resolution of the index tophi occurred in 18 (69%) subjects by Final Visit. Resolution of index tophi throughout the duration of the study is shown in Fig. 3.

When analysed individually by age, gender, BMI at baseline, baseline uric acid production status, tophi present at baseline, or history of kidney stones, there were no significant differences in the urate-lowering efficacy of febuxostat between the levels of the above factors. In addition, there was no significant relationship between renal function and the urate-lowering efficacy of febuxostat in the group of subjects with mild to moderate renal impairment. Across the visits, the percent of subjects with normal renal function attaining sUA <6.0 mg/dl was 72–92% compared with 75–97% for subjects with impaired renal function. However, a statistically significant difference in urate-lowering efficacy of febuxostat was observed when Caucasian and non-Caucasian subjects were compared: 87% of Caucasian subjects achieved sUA <6.0 mg/dl at Final Visit compared with 65% of non-Caucasian subjects (P = 0.025).

Safety results

AEs were reported by 91% (106/116) of the subjects during the study. The most frequently reported AEs (occurred in ≥10% of total subjects) by study drug dose at the time of occurrence are shown in Table 3. The majority of AEs were mild or moderate in severity. In general, there were no increases in the incidence of AEs over time. AEs were analysed by the dose at the time of the event; as such, subjects that switched doses could be included in more than one treatment group. Due to imbalance of treatment exposure, AEs by dose were summarized by patient-year (PY) of exposure. There were 349 AEs per 100 PYs overall, with 273.5, 384.7 and 258.7 events per 100 PYs among subjects who received febuxostat 40, 80 and 120 mg, respectively.

Serious AEs were reported by 18% (21/116) of the subjects; the majority resulted in hospitalization. Five subjects experienced atrial fibrillation while on febuxostat 80 mg/day; atrial fibrillation was the most frequently reported serious AE. The investigators did not attribute any of the serious AEs to the study drug. No myocardial infarctions occurred during the study. Alternate aetiologies for atrial fibrillation, as proposed by the investigators, were non-cardiac rhythm disturbances including sinus tachycardia, supraventricular tachycardia, and atrial flutter. Among prior cardiovascular events, 27 of 116 subjects (23%) had a recorded history of atrial fibrillation.
During the study.
and Alzheimer’s-related dementia (each non-cardiac chest pain, renal impairment, spondylitic myelopathy
subjects with abnormal LFTs had elevated values at baseline prior to study drug treatment. These resolved within 10–106 days. All
n
Serious AEsa

Table 3. Adverse events

<table>
<thead>
<tr>
<th>All subjects</th>
<th>N=116, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most frequently reported (≥10%) AEs*</td>
<td>Total subjects with at least 1 AE</td>
</tr>
<tr>
<td></td>
<td>106 (91)</td>
</tr>
<tr>
<td>Upper respiratory tract infections</td>
<td>61 (53)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue signs and symptoms</td>
<td>42 (36)</td>
</tr>
<tr>
<td>Joint-related signs and symptoms</td>
<td>33 (28)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>24 (21)</td>
</tr>
<tr>
<td>Influenza</td>
<td>20 (17)</td>
</tr>
<tr>
<td>Limb injuries</td>
<td>20 (17)</td>
</tr>
<tr>
<td>Headache</td>
<td>18 (16)</td>
</tr>
<tr>
<td>Paresthesias and dysesthesias</td>
<td>16 (14)</td>
</tr>
<tr>
<td>Lower respiratory tract and lung infections</td>
<td>15 (13)</td>
</tr>
<tr>
<td>Liver function analyses</td>
<td>15 (13)</td>
</tr>
<tr>
<td>Vascular hypertensive disorders</td>
<td>15 (13)</td>
</tr>
<tr>
<td>Gastrointestinal and abdominal pains</td>
<td>14 (12)</td>
</tr>
<tr>
<td>Rash, eruptions and exanthems</td>
<td>14 (12)</td>
</tr>
<tr>
<td>Skin injuries</td>
<td>13 (11)</td>
</tr>
<tr>
<td>Osteoarthropathies</td>
<td>13 (11)</td>
</tr>
<tr>
<td>Oedema</td>
<td>12 (10)</td>
</tr>
<tr>
<td>Pain and discomfort</td>
<td>12 (10)</td>
</tr>
<tr>
<td>Non-site-specific injuries</td>
<td>12 (10)</td>
</tr>
<tr>
<td>Tendon disorders</td>
<td>12 (10)</td>
</tr>
</tbody>
</table>

Pain and discomfort 12 (10)
Oedema 12 (10)
Osteoarthropathies 13 (11)
Skin injuries 13 (11)
Oedema 12 (10)
Pain and discomfort 12 (10)
Non-site-specific injuries 12 (10)
Tendon disorders 12 (10)

Serious AEsa

Total subjects with at least 1 serious AE 21 (18)
Cardiac disorders (atrioventricular block; atrial fibrillation) 6 (5)
Gastrointestinal disorders (small intestinal obstruction; diverticular perforation; appendicitis perforated) 3 (3)
General disorders and administration site conditions (non-cardiac chest pain) 1 (<1)
Hepatobiliary disorders (cholecystitis) 2 (2)
Infections and infestations (diverticulitis; pneumonia; urosepsis) 4 (3)
Injury, poisoning and procedural complications (conceussion; traumatic fracture; excoriation; radiation injury) 3 (3)
Musculoskeletal and connective tissue disorders (intervertebral disc degeneration; rotator cuff syndrome; OA; osteoporotic fracture; lumbar spinal stenosis) 5 (4)
Neoplasms benign, malignant and unspecified (malignant tongue neoplasm; prostate cancer; benign lung neoplasm; basal cell carcinoma) 4 (3)
Nervous system disorders (Alzheimer; cerebrovascular accident) 2 (2)
Psychiatric disorders (depression) 1 (<1)
Renal and urinary disorders (urinary retention) 1 (<1)

*Classified by MedDRA high-level terms. bClassified by system organ class (preferred term).

Medical histories, included concomitant medication use, dehydration, cellulitis and possible acute coronary syndrome and cardiovascular disease. A complete list of serious AEs is included in Table 3.

Thirteen subjects reported an AE as a primary reason for premature discontinuation. The most common AEs that led to withdrawal from the study were abnormal liver function tests (LFTs; n = 3), cancers (n = 3) and increased serum creatinine (n = 2). Of these AEs, all three instances of abnormal LFTs and one instance of increased serum creatinine were considered related to the study drug treatment. These resolved within 10–106 days. All subjects with abnormal LFTs had elevated values at baseline prior to exposure to febuxostat, and two subjects reported regular use of alcohol (10 drinks per week). Additional AEs that led to discontinuation included increased frequency of bowel movements, non-cardiac chest pain, renal impairment, spondylitic myelopathy and Alzheimer’s-related dementia (each n = 1). No deaths occurred during the study.

Discussion

Reduction to and maintenance of sUA <6.0 mg/dl (<360 μmol/l), a range below the limit of solubility of urate in serum, is a widely

recommended treatment goal in the management of hyperuricaemia in subjects with gout [7, 9, 20]. Maintenance of sUA in this range has resulted in clinical benefits of tophus resolution and decreased gout flare incidence over the long term [3, 6–8, 21, 22]. The ability of febuxostat to lower and maintain sUA <6.0 mg/dl for up to 5 yrs has been demonstrated in this study, which represents the longest febuxostat study to date and one of the few long-term studies reported for any urate-lowering therapy [8, 23]. Continued treatment with febuxostat resulted in a decline in the incidence of gout flares that required treatment (Fig. 2). After 5 yrs of urate-lowering therapy with febuxostat, the number of subjects that remained in the study that experienced gout flares declined to zero. Long-term maintenance of sUA <6.0 mg/dl also resulted in the resolution of baseline tophi in the majority of subjects. Similar results in tophus reduction have been reported elsewhere [8].

Acute gout flares frequently occurred during the first few months of urate-lowering treatment, and prophylactic treatment with colchicine or NSAIDs was recommended when urate-lowering therapy was initiated [20, 24]. The observed increase in gout flares after prophylaxis withdrawal was followed by a stepwise decrease in the percentage of subjects that reported flares, presumably related to continued reduction of body urate pools. In previously reported Phase 3 trials [18, 19], prophylaxis for gout flares was provided for the first 8 weeks, while subjects in this study received colchicine for 4 weeks. The shorter duration of prophylaxis may have contributed to a higher incidence of gout flares during the first 6 months than might have been observed if prophylaxis had been extended.

The success of urate-lowering therapy depends on long-term adherence to medication in order to achieve and maintain an optimal sUA. In several studies, adherence to allopurinol has been poor [22, 25, 26], resulting in failure to achieve sUAs <6.0 mg/dl and failure to reduce rates of gout flare. Furthermore, additional studies suggest that many subjects receive sub-optimal management with urate-lowering therapy for gout/hyperuricaemia [27–29].

Significantly higher febuxostat efficacy was observed in Caucasian subjects compared with non-Caucasian subjects. However, the total number of non-Caucasian subjects was small (n = 17), which indicates the need for further investigation involving greater numbers of minority subjects. It is especially important to determine the efficacy of febuxostat in these populations, as black men may be more likely to have gout than Caucasian men [30]. In addition, higher rates of hyperuricaemia and gout in other non-Caucasian populations, often in particular geographic regions, such as the Maoris of New Zealand, are well known [31].

No significant difference in the urate-lowering efficacy of febuxostat was observed between subjects with normal and impaired renal function. Mild to moderate renal impairment has little impact on the pharmacodynamics and pharmacokinetics of febuxostat [32–34], and the safety of this drug in these circumstances has been satisfactory to date. Further studies are needed to assess safety in such subjects over longer periods of time and to assess safety in individuals with more advanced kidney disease.

The majority of AEs were reported as mild to moderate in severity. Thirteen subjects prematurely discontinued due to an AE. No hypersensitivity reactions were observed. Investigators considered all serious AEs unrelated to the study drug. However, this assessment was subjective and no placebo or active comparator, as used in previous studies [18, 19], was included in this study to truly determine if an AE was or was not likely to be related to the study drug.

Some limitations need to be considered when interpreting the results of this study. Fifty percent of subjects prematurely discontinued, possibly skewing the results towards a greater reduction in gout flares. The reduction in the number of patients
may negatively impact the power of the subanalyses, and additional studies with greater numbers of subjects are needed to verify the trends described. This discontinuation rate may reflect clinical reality. The retention rate reported here is far higher than the rate observed in a retrospective analysis of almost 6000 subjects with gout in a managed care cohort. This retrospective analysis found that among those prescribed allopurinol for urate-lowering therapy, the mean duration of continuous treatment was 8.5 months (±11 months) and 87.1% discontinued treatment during the 5 yrs for which data were available [26]. The relatively high level of adherence in this study might have been influenced by frequent follow-up and monitoring over the course of the trial.

Another potential limitation was the assessment of flares and tophi. Flares are an important outcome in this study, but a method to validate flares is still needed. Here, assessment of flares relied on self-reports and confirmation by documentation of treatment. Studies addressing gout outcome measures and validation are currently underway [35]. Assessment of tophi resolution was subjective and determined by individual investigators. An easy, reproducible method for measuring tophi has been reported [36], and future investigators may want to consider employing this technique when following tophi regression or growth.

Patients were often on treatments for comorbidities. While some anti-hyperuricemic and anti-hyperlipidemia agents are known to affect sUA [9], the use of these medications during the study should not have introduced any systematic error. As subjects were not randomized to dose groups and dose titration was allowed, meaningful comparisons between dose groups is not possible. In addition, while clinical benefit from long-term febuxostat therapy is clearly demonstrated, there is no control or comparator group to establish how therapy with febuxostat compares with currently employed urate-lowering regimens with regard to clinical outcomes. Shorter duration (up to 1 yr) trials have demonstrated that febuxostat is significantly better than allopurinol (300 mg) in lowering sUA [18, 19], but longer term studies comparing various doses of febuxostat and allopurinol are needed to establish the relative urate lowering and clinical benefits of these agents.

The findings of this long-term study in subjects with gout indicate that treatment with febuxostat for up to 5 yrs results in a sustained reduction in sUA. Subjects that maintain an sUA <6.0 mg/dl have infrequent gout flares and reduction in the presence of tophi.

Rheumatology key messages

- Long-term treatment with febuxostat resulted in durable maintenance of sUA <6.0 mg/dl for most subjects.
- There was nearly complete abolition of gout flares.
- Baseline tophi resolved in a majority of subjects.

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