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ORIGINAL ARTICLE

Effects of Febuxostat Versus Allopurinol and Placebo in Reducing Serum Urate in Subjects With Hyperuricemia and Gout: A 28-Week, Phase III, Randomized, Double-Blind, Parallel-Group Trial

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Objective. **To compare the urate-lowering efficacy and safety of febuxostat, allopurinol, and placebo in a large group of subjects with hyperuricemia and gout, including persons with impaired renal function.**

Methods. **Subjects (n = 1,072) with hyperuricemia (serum urate level ≥8.0 mg/dl) and gout with normal or impaired (serum creatinine level >1.5 to ≤2.0 mg/dl) renal function were randomized to receive once-daily febuxostat (80 mg, 120 mg, or 240 mg), allopurinol (300 or 100 mg, based on renal function), or placebo for 28 weeks.**

Results. **Significantly ($P \leq 0.05$) higher percentages of subjects treated with febuxostat 80 mg (48%), 120 mg (65%), and 240 mg (69%) attained the primary end point of last 3 monthly serum urate levels <6.0 mg/dl compared with allopurinol (22%) and placebo (0%). A significantly ($P < 0.05$) higher percentage of subjects with impaired renal function treated with febuxostat 80 mg (4 [44%] of 9), 120 mg (5 [45%] of 11), and 240 mg (3 [60%] of 5) achieved the primary end point compared with those treated with 100 mg of allopurinol (0 [0%] of 10). Proportions of subjects experiencing any adverse event or serious adverse event were similar across groups, although diarrhea and dizziness were more frequent in the febuxostat 240 mg group. The primary reasons for withdrawal were similar across groups except for gout flares, which were more frequent with febuxostat than with allopurinol.**

Conclusion. **At all doses studied, febuxostat more effectively lowered and maintained serum urate levels <6.0 mg/dl than did allopurinol (300 or 100 mg) or placebo in subjects with hyperuricemia and gout, including those with mild to moderately impaired renal function.**

INTRODUCTION

The primary goal in managing patients with hyperuricemia and gout is to reduce or reverse the expression of clinical events by lowering and maintaining serum urate levels below the limit of urate solubility (approximately 6.8 mg/dl) (1–9). Lowering serum urate below saturating levels (<6.0 mg/dl, 0.36 mmoles/liter) over time results in

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reduced frequency of acute gouty attacks (flares) (5,10–13) and reduced size and/or number of clinically detectable urate crystal deposits (tophi) (4,10,14).

For most gout patients with repeated acute flares of gouty arthritis, chronic gouty arthropathy, tophi, or uric acid urolithiasis, long-term maintenance of serum urate levels <6.0 mg/dl requires urate-lowering pharmacotherapy (2,15–17). Two classes of drug agents are currently available for this purpose: uricosuric agents, which increase renal excretion of uric acid, and xanthine oxidase inhibitors, which reduce urate synthesis. For many years, the most commonly employed urate-lowering agent in the US has been allopurinol, a hypoxanthine analog. Although allopurinol is generally safe and effective, it can occasionally induce life-threatening rashes and/or a severe multisystem allopurinol hypersensitivity syndrome (18–20). Furthermore, the prolonged half-life (14–26 hours) of the major allopurinol active oxidation product, oxypurinol, and its further prolongation in patients with decreased creatinine clearance has prompted dose reduction in patients with impaired renal function (19,21,22).

Febuxostat, an orally administered nonpurine selective inhibitor of xanthine oxidase, is in development for the management of hyperuricemia in patients with gout. In contrast to allopurinol, febuxostat inhibits both oxidized and reduced forms of xanthine oxidase (23,24) and has minimal effects on other enzymes of purine and pyrimidine metabolism (24,25). After oral administration, febuxostat is rapidly and extensively (84%) absorbed (26), with a half-life ranging from 4–18 hours for doses between 10 and 120 mg (27–29). Febuxostat undergoes hepatic metabolism with approximately one-half of administered febuxostat (unchanged drug and metabolites) excreted in the stool and the remainder appearing in the urine (27).

Short-term pharmacokinetic studies performed in nongouty subjects with impaired renal function (30,31) suggest that febuxostat dose adjustment may not be required in these patients. In previous trials conducted in healthy volunteers and subjects with gout and hyperuricemia (10,15,27), febuxostat exhibited potent and dose-dependent urate-lowering efficacy. However, none of these trials were intended to examine the efficacy or safety of febuxostat in subjects with impaired renal function, hyperuricemia, and gout.

The objective of this multicenter, Allopurinol- and Placebo-Controlled, Efficacy Study of Febuxostat (APEX) trial was to compare the safety and efficacy of orally administered febuxostat with placebo and allopurinol in subjects with hyperuricemia and gout. Furthermore, this study sought to confirm and expand upon the results observed in the Febuxostat versus Allopurinol Controlled Trial (FACT) (10) by assessing the effects of treatment in subjects with impaired renal function (serum creatinine level >1.5 to ≤2.0 mg/dl).

SUBJECTS AND METHODS

Study population. This phase III, randomized, double-blind, allopurinol- and placebo-controlled, parallel-group trial was conducted at 167 sites in the US. The majority of investigators were primary care physicians. Institutional review boards at participating sites approved the protocol and written informed consent that conformed to the Declaration of Helsinki and the Health Insurance Portability and Accountability Act. Written consent was obtained from all subjects prior to any study-related procedures. Eligible participants were of either sex and 18–85 years of age, inclusive, with gout (defined by the American College of Rheumatology preliminary criteria [32]), hyperuricemia (defined for this study as a serum urate level ≥8.0 mg/dl), and normal (serum creatinine level ≤1.5 mg/dl) or impaired (serum creatinine level >1.5 to ≤2.0 mg/dl) renal function at day −2. Exclusion criteria included intolerance to allopurinol, naproxen, or colchicine; history of renal calculi; alcohol intake of ≥14 drinks/week; hepatic dysfunction with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) both >1.5 times the upper limit of normal; or any other significant medical conditions.

After a 2-week washout period for those receiving previous urate-lowering therapy, subjects were randomized in a 2:2:1:2:1 ratio to once-daily febuxostat 80 mg, febuxostat 120 mg, febuxostat 240 mg, allopurinol, or placebo. The randomization was stratified by renal function. Allopurinol dose was dependent on renal function; subjects with normal renal function (serum creatinine level ≤1.5 mg/dl, n = 258) received 300 mg, whereas subjects with renal impairment (serum creatinine level >1.5 to ≤2.0 mg/dl, n = 10) received 100 mg based on Food and Drug Administration–approved dosing information (21). Results from these 2 allopurinol doses were analyzed together, and are referred to as allopurinol unless otherwise noted. There was no dose adjustment in the febuxostat treatment arms. Either colchicine 0.6 mg once daily or naproxen 250 mg twice daily was provided during the washout period for subjects receiving prior urate-lowering therapies or upon randomization for subjects not receiving prior urate-lowering therapy, and was continued for the first 8 weeks of the study as prophylaxis for gout flares. The investigator used his or her judgment in selecting between naproxen and colchicine, although colchicine was recommended for subjects with a serum creatinine level >1.5 mg/dl. Any gout flares occurring during the first 8 weeks or later were treated at the investigator's discretion. Serum urate levels, laboratory assessments, gout flares, adverse events (AEs), concomitant medications, and number and size of palpable tophi were monitored at visits every 4 weeks.

Efficacy end points. The primary end point was the proportion of subjects with the last 3 monthly serum urate levels <6.0 mg/dl. The last 3 serum urate levels for each subject, regardless of whether or not the subject completed the study, were used to determine if the subject was a responder. If a subject discontinued the study before ≥3 serum urate levels were obtained, the subject was considered a nonresponder. Secondary end points included the proportion of subjects with a serum urate level <6.0 mg/dl at each visit, the percent reduction of serum urate from baseline at each visit, the proportion of subjects requiring treatment for a self-reported gout flare between weeks 8

and 28, reduction in the number of tophi at each visit for subjects with palpable tophi at baseline, and the percent reduction in primary tophus size at each visit in those subjects with a primary palpable tophus at baseline. Primary tophi were physically measured by the investigator or designee according to a published method (33). For variables summarized by visit, data are shown for both the week 28 visit and the final visit (defined as each subject's last postbaseline visit).

Statistical analysis. All efficacy analyses were performed on the intent-to-treat population, defined as all randomized subjects who received ≥1 dose of study drug and had a serum urate level ≥8.0 mg/dl at baseline. Comparisons for the primary efficacy end point were made sequentially using a 3-step closed testing process. First, each febuxostat group was compared with placebo for superiority using a Cochran-Mantel-Haenszel (CMH) test (stratified by baseline renal function) with Hochberg's method for multiple comparisons to ensure that the overall P value was <0.05 (34). Second, if each dose of febuxostat was shown to be superior to placebo, the febuxostat 80 mg and 120 mg groups were tested for noninferiority to allopurinol using binomial confidence intervals. Noninferiority was declared if the lower limit of the 97.5% confidence interval for the difference in response rates was greater than −10%. Finally, each dose of febuxostat shown to be noninferior to allopurinol was tested for superiority to allopurinol using a CMH test stratified by baseline renal function with Hochberg's method for multiple comparisons. Post hoc pairwise comparisons within the subgroups of subjects with renal impairment and subjects with normal renal function were made using Fisher's exact test.

Pairwise comparisons between groups for the secondary efficacy end points were made using a CMH test (stratified by baseline renal function) for the proportion of subjects with serum urate levels <6.0 mg/dl at the week 28 and final visits, and the proportion of subjects requiring treatment for a gout flare between weeks 8 and 28 and during the prophylaxis period. An analysis of variance for the percent reduction from baseline in serum urate levels at week 28 and final visits was performed. Wilcoxon's rank sum test was performed for the percent reduction in primary tophus size and reduction in number of tophi at week 28 and final visits. Demographic data were analyzed for differences among groups, using analysis of variance for continuous variables and chi-square test for categorical variables. Fisher's exact test was used for pairwise comparison of AEs, liver function test elevations, and primary reason for withdrawal between the groups.

A sample size of 1,000 subjects was targeted to provide ≥80% power to meet noninferiority criteria between febuxostat and allopurinol, ≥95% power to detect a ≥45% difference between each febuxostat group and placebo, and ≥90% power to detect a 15% difference between ≥1 febuxostat group and the allopurinol group for the primary end point. The unequal randomization ratio was chosen because a larger number of subjects was required to show noninferiority between the febuxostat 80 mg and 120 mg groups and the allopurinol group than to show a difference between febuxostat and placebo. Since febuxostat 240 mg was included for safety assessment only, comparisons of this febuxostat dose with allopurinol were not powered.

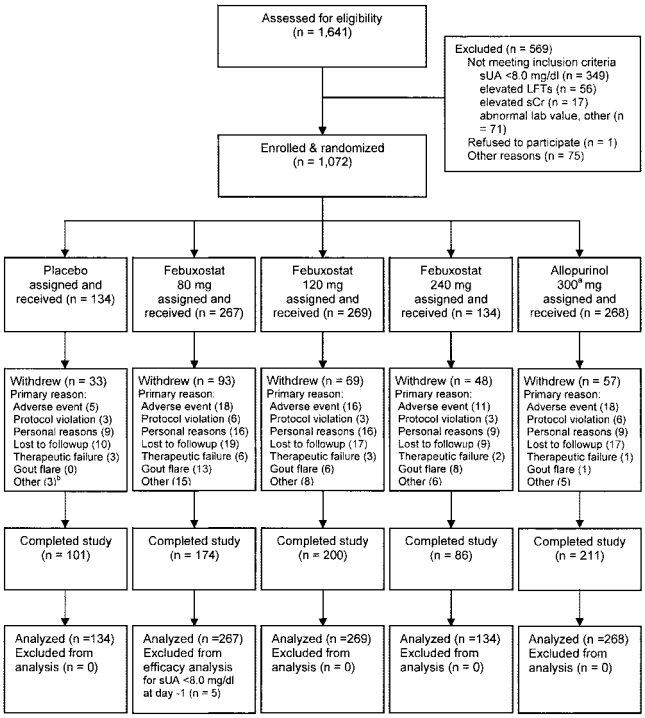

Figure 1. Subject disposition. sUA = serum urate level; LFTs = liver function tests; sCr = serum creatinine; [a] = Ten subjects received 100 mg and 258 subjects received 300 mg of allopurinol based on renal function; [b] = Other, as a primary reason for withdrawal most often included noncompliance or withdrawal of consent.

Analyses were performed with SAS statistical software, version 8.2 (SAS Institute, Cary, NC) with the UNIX operating system. All statistical tests and confidence intervals were 2-sided and P values less than or equal to 0.05 were considered to be statistically significant, unless otherwise specified.

RESULTS

Subject disposition. Between February 2003 and April 2004, 1,072 subjects participated in this 28-week, double-blind, allopurinol- and placebo-controlled study (Figure 1). Five subjects randomized to febuxostat 80 mg were excluded from the efficacy analyses because they did not meet the inclusion criteria of a serum urate level ≥8.0 mg/dl on day −1. Premature withdrawal rates were higher in the febuxostat 80 mg and 240 mg groups (35% and 36%, respectively) than in the febuxostat 120 mg (26%) or allopurinol (21%) groups ($P \leq 0.05$). The withdrawal rate was also higher in the febuxostat 80 mg group than in the placebo group (25%; $P \leq 0.05$). The majority of withdrawals from each group (58–69% of withdrawals) occurred within the first 12 weeks of the study. Primary reasons for withdrawal were similar across all treatment groups except for gout flares, which were more frequently reported with febuxostat, and significantly so ($P = 0.001$) in the

Table 1. Baseline characteristics and gout disease history of randomized subjects*

Characteristic	Placebo (n = 134)	Febuxostat 80 mg (n = 267)	Febuxostat 120 mg (n = 269)	Febuxostat 240 mg (n = 134)	Allopurinol 300 mg (n = 268)†
Age, mean ± SD years	52 ± 12	51 ± 12	51 ± 12	54 ± 13	52 ± 12
Male, %	92	94	95	94	93
Race					
White	108 (81)	200 (75)	214 (80)	107 (80)	206 (77)
Minority	26 (19)	67 (25)	55 (20)	27 (20)	62 (23)
BMI, mean ± SD kg/m^2	32 ± 6	33 ± 6	33 ± 7	33 ± 7	33 ± 6
Hypercholesterolemia	8 (6)	12 (5)	17 (6)	8 (6)	16 (6)
Hyperlipidemia	44 (33)	90 (34)	90 (33)	49 (37)	76 (28)
Hypertension	61 (46)	124 (46)	124 (46)	70 (52)	123 (46)
Cardiovascular disease	18 (13)	38 (14)	37 (14)	24 (18)	27 (10)
Gout history, mean ± SD years	10 ± 8	11 ± 9	12 ± 9	11 ± 9	11 ± 9
History/presence of tophi	44 (33)	62 (24)	79 (30)	36 (27)	76 (28)
Recent use of allopurinol (within 30 days of randomization)	27 (20)	83 (31)	84 (31)	44 (33)	78 (29)
Low-dose aspirin use	30 (22)	46 (17)	39 (14)	34 (25)	34 (13)
Mild to moderate renal impairment‡	5 (4)	9 (3)	11 (4)	5 (4)	10 (4)

* Values are the number (percentage) unless otherwise indicated. BMI = body mass index.
† Ten subjects received 100 mg and 258 subjects received 300 mg of allopurinol based on renal function.
‡ Serum creatinine level >1.5 to ≤2.0 mg/dl.

febuxostat 80 mg and 240 mg treatment groups versus allopurinol (Figure 1).

Baseline characteristics. The majority of subjects were male (94%), white (78%), and age 45–65 years (56%). At baseline, the mean duration of gout was 10.9 years, with 89% of subjects experiencing a gout flare within the past year. Twenty percent of subjects had a primary palpable tophus. Tophi had been present for an average of 5.7 years for those with tophi or a history of tophi at baseline. Forty-seven percent of subjects had hypertension, 33% hyperlipidemia, 62% obesity (body mass index ≥30 kg/m^2), 4% impaired renal function (serum creatinine level >1.5 to ≤2.0 mg/dl), 66% a current history of alcohol use (<14 drinks/week), and 13% cardiovascular disease. Mean ± SD baseline serum urate level was 9.85 ± 1.263 mg/dl, with 39% of subjects having a baseline serum urate level ≥10.0 mg/dl. Baseline characteristics, comorbidities, and gout history did not differ significantly across treatment groups (Table 1). Mean study drug compliance was similar among all treatment groups and ranged from 95.8–97.8%.

Efficacy analysis. *Proportion of subjects with last 3 monthly serum urate levels <6.0 mg/dl.* A significantly ($P < 0.001$) greater proportion of subjects receiving febuxostat at any dose achieved the primary end point of last 3 monthly serum urate levels <6.0 mg/dl than subjects receiving allopurinol or placebo (Figure 2). Allopurinol also produced significantly ($P < 0.001$) greater percent decreases in serum urate level from baseline than placebo. Among subjects with a baseline serum urate level ≥10.0 mg/dl, 36%, 52%, and 66% of subjects achieved last 3 serum urate levels <6.0 mg/dl while receiving febuxostat 80 mg, 120 mg, and 240 mg, respectively. In contrast, few (10%) of these subjects achieved last 3 serum urate levels <6.0 mg/dl while receiving allopurinol. Interestingly, the response rate in subjects receiving allopurinol who reported prior allopurinol use was nearly identical to the rate in those who reported no prior allopurinol use (22.6% versus 22.2%). The proportions of subjects with impaired renal function (serum creatinine level >1.5 to ≤2.0 mg/dl) attaining last 3 monthly serum urate levels <6.0 mg/dl were 44% in the febuxostat 80 mg group, 46% in the 120 mg group, and 60% in the 240 mg group. No subject with

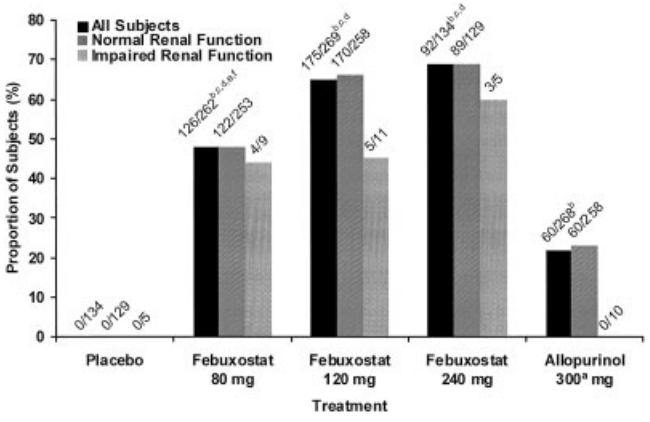

Figure 2. Proportion of subjects with last 3 monthly serum urate levels <6.0 mg/dl (intent-to-treat population). The treatment groups that were statistically significantly different for all subjects were also statistically significantly different for the subset of subjects with normal renal function. [a] = Ten subjects received 100 mg and 258 subjects received 300 mg of allopurinol based on renal function; [b] = Statistically significant ($P < 0.001$) versus placebo in all subjects; [c] = Statistically significant ($P < 0.05$) versus allopurinol in subjects with impaired renal function; [d] = Statistically significant ($P < 0.001$) versus allopurinol in all subjects; [e] = Statistically significant ($P < 0.001$) versus febuxostat 120 mg in all subjects; [f] = Statistically significant ($P < 0.001$) versus febuxostat 240 mg in all subjects.

Table 2. Proportion of subjects with serum urate levels <6.0 mg/dl at week 28 and final visits (intent-to-treat population)

	Week 28, %	Final, %
Placebo	1 (1/99)	1 (1/127)
Febuxostat 80 mg	76 (122/161)*	72 (183/253)*
Febuxostat 120 mg	87 (163/188)†	79 (209/265)*
Febuxostat 240 mg	94 (78/83)†	92 (116/126)‡
Allopurinol 300 mg§	41 (85/208)¶	39 (102/263)¶

* Statistically significant versus placebo ($P \leq 0.05$) and versus allopurinol ($P \leq 0.05$).
† Statistically significant versus placebo ($P \leq 0.05$), versus allopurinol ($P \leq 0.05$), and versus febuxostat 80 mg ($P \leq 0.05$).
‡ Statistically significant versus placebo ($P \leq 0.05$), versus allopurinol ($P \leq 0.05$), versus febuxostat 80 mg ($P \leq 0.05$), and versus febuxostat 120 mg ($P \leq 0.05$).
§ Ten subjects received 100 mg and 258 subjects received 300 mg of allopurinol based on renal function.
¶ Statistically significant versus placebo ($P \leq 0.05$).

renal impairment receiving allopurinol 100 mg or placebo achieved last 3 monthly serum urate levels <6.0 mg/dl (Figure 2).

Proportion of subjects with serum urate level <6.0 mg/dl at week 28 or final visit. At the week 28 visit, 76% of subjects treated with febuxostat 80 mg, 87% with febuxostat 120 mg, and 94% with febuxostat 240 mg achieved serum urate levels <6.0 mg/dl, whereas 41% of those treated with allopurinol and 1% of those treated with placebo achieved the same goal (Table 2). Similar success rates were seen at the final visit. None (0 of 10) of the subjects with renal impairment who received allopurinol 100 mg attained serum urate levels <6.0 mg/dl at either the week 28 or final visits.

Percent reduction in serum urate level. At both the week 28 and final visits, all febuxostat doses produced significantly ($P \leq 0.05$) greater percent decreases in serum urate levels from baseline (−48% and −45% for 80 mg, −55% and −52% for 120 mg, and −68% and −66% for 240 mg at week 28 and final visits, respectively) compared with allopurinol (−34% and −34%, respectively) and placebo (−4% and −3%, respectively). Reductions in serum urate levels were evident at week 2 and persisted throughout the study.

Proportion of subjects requiring treatment for gout flare. Between weeks 8 (after the prophylaxis period) and 28, there were no statistically significant differences in the proportion of subjects requiring treatment for gout flares observed between the treatment groups; the proportion of subjects requiring treatment for gout flares tended to diminish with continued treatment. In contrast, during the first 8 weeks of the study, when gout flare prophylaxis was provided, greater proportions ($P \leq 0.05$) of subjects receiving febuxostat 120 mg (97 [36%] of 269) and 240 mg (69 [46%] of 134) required treatment for gout flares compared with those receiving febuxostat 80 mg (73 [28%] of 262), allopurinol (61 [23%] of 268), or placebo (27 [20%] of 134).

Total number and size of tophi. No significant differences in the number of tophi were observed between treatment groups, with the exception of a mean percent decrease in the number of tophi observed with febuxostat 120 mg (−1.2) versus placebo (−0.3) at week 28 ($P \leq 0.05$). Reductions in median tophus size from baseline were reported in each treatment group, including placebo; however, there were no significant differences between treatments.

Safety analysis. *Adverse events.* Generally, AEs occurred with similar frequency across treatment groups and were mild or moderate in severity. The most frequently reported AEs (≥5% of subjects) are listed in Table 3. A statistically significant increase in the incidence of diarrhea was seen in the febuxostat 240 mg group compared with each of the other active treatment groups, but not with placebo. The incidence of hypertension was significantly higher for subjects treated with febuxostat 80 mg compared with subjects treated with allopurinol, but not with placebo. An increased incidence of hypertension was not seen for the other 2 doses of febuxostat when compared with either allopurinol or placebo. The reported occurrence of dizziness was significantly greater in subjects receiving febuxostat 240 mg when compared with subjects receiving febuxostat 80 or 120 mg or allopurinol; however, the incidence was not significantly higher in any active treatment group when compared with placebo.

AEs related to abnormal findings on liver function tests, designated as such by individual investigators, were reported for a total of 51 subjects: 17 (6%) receiving febuxostat 80 mg, 10 (4%) receiving febuxostat 120 mg, 6 (4%) receiving febuxostat 240 mg, 15 (6%) receiving allopurinol, and 3 (2%) receiving placebo. Of these subjects, 12 withdrew due to this AE: 5 receiving febuxostat 80 mg, 3 receiving febuxostat 120 mg, and 4 receiving allopurinol (Table 3). These events were classified by the investigator as mild to moderate in severity, and only 1 was not transient. This subject (receiving febuxostat 80 mg) had concurrent hepatitis C and entered the study with elevated hepatic enzymes (day −6) that persisted and led to premature discontinuation at day 53. In addition to these liver function test AEs, the proportions of subjects with 1 or more concurrent ALT and AST value ≥1.5 times the upper limit of normal are shown in Table 4.

All rash-related AEs (i.e., allergic, contact, and exfoliative dermatitis; heat, erythematous, follicular, macular, maculopapular, papular, pruritic, and scaly rashes; eczema; erythema; rash, not elsewhere classified; and urticaria) were combined to assess if there were any differences among treatment groups. These combined terms of rash-related events were reported with similar incidence in all treatment groups: 5% (14 of 267) receiving febuxostat 80 mg, 6% (17 of 269) receiving febuxostat 120 mg, 4% (6 of 134) receiving febuxostat 240 mg, 5% (14 of 268) receiving allopurinol, and 5% (7 of 134) receiving placebo. However, none of the individual types of rashes occurred at a rate that qualified as a frequently reported AE (≥5% of subjects in any group). Eight subjects withdrew due to any of these rash types: 3 receiving febuxostat 80 mg, 3 receiving febuxostat 120 mg, 0 receiving febuxostat 240 mg, 1 receiving allopurinol, and 1 receiving placebo. Most rash events were mild or moderate in severity, although 2 subjects reported severe rashes while receiving febuxostat 80

Table 3. Adverse events (AEs)*

	Placebo (n = 134)	Febuxostat 80 mg (n = 267)	Febuxostat 120 mg (n = 269)	Febuxostat 240 mg (n = 134)	Allopurinol 300 mg (n = 268)†
Any AE	97 (72)	181 (68)	183 (68)	98 (73)	200 (75)
Most frequent AEs‡					
Upper respiratory tract infections	21 (16)	39 (15)	52 (19)	27 (20)	52 (19)
Musculoskeletal and connective tissue signs and symptoms§	13 (10)	23 (9)	24 (9)	14 (10)	27 (10)
Diarrhea	11 (8)	16 (6)¶	19 (7)¶	18 (13)#	17 (6)
Joint-related signs and symptoms§	7 (5)	17 (6)	23 (9)	7 (5)	20 (7)
Headaches	7 (5)	14 (5)	14 (5)	12 (9)	19 (7)
Abnormal findings on liver function test (designated as AE by investigator)**	3 (2)	17 (6)	10 (4)	6 (4)	15 (6)
Influenza viral infections	6 (4)	11 (4)	13 (5)	7 (5)	10 (4)
Nausea and vomiting symptoms	5 (4)	12 (4)	10 (4)	8 (6)	6 (2)
Non–site-specific injuries	3 (2)	11 (4)	9 (3)	9 (7)	8 (3)
Vascular hypertensive disorders (hypertension)	8 (6)	13 (5)#	6 (2)	6 (4)	3 (1)††
Gastrointestinal and abdominal pains (excluding oral and throat)	3 (2)	6 (2)	7 (3)	8 (6)	6 (2)
Neurologic signs and symptoms (dizziness)	2 (1)	5 (2)¶	5 (2)¶	9 (7)#	6 (2)
Muscle-related signs and symptoms (muscle cramps, muscle twitching, night cramps)	7 (5)	3 (1)††	2 (<1)††	2 (1)	1 (<1)††
Serious AEs	2 (1)	11 (4)	9 (3)	5 (4)	7 (3)
Cardiovascular events (chest pain, coronary artery disease, myocardial infarction, atrial fibrillation)	1 (<1)	5 (2)	5 (2)	1 (<1)	1 (<1)
AEs leading to withdrawal‡‡	7 (5)	21 (8)	19 (7)	13 (10)	18 (7)
Abnormal findings on liver function test**	0	5 (2)	3 (1)	0	4 (1)
Diarrhea	0	2 (<1)	1 (<1)	4 (3)§§	1 (<1)
Serious AEs leading to withdrawal	0	3 (1)	5 (2)	0	1 (<1)
Cardiovascular disorders (coronary artery disease, acute coronary syndrome, myocardial infarction)	0	1 (<1)	2 (<1)	0	0
Cancer (malignant parathyroid tumor, Hodgkin's disease)	0	0	1 (<1)	0	1 (<1)
Miscellaneous (pleuritic pain, nausea, muscular weakness, vomiting, anemia, hypoglycemic seizure)	0	2 (<1)	2 (<1)	0	0

* Values are the number (percentage).
† Ten subjects received 100 mg and 258 subjects received 300 mg of allopurinol based on renal function.
‡ AEs occurring in ≥5% of subjects in any group.
§ Excluding gout flares, which were not considered an AE.
¶ Statistically significant versus febuxostat 240 mg ($P \leq 0.05$).
# Statistically significant versus allopurinol ($P \leq 0.05$).
** Terms that are included: alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, hepatic enzyme increased, abnormal findings on liver function tests, transaminases increased.
†† Statistically significant versus placebo ($P \leq 0.05$).
‡‡ AEs listed as primary or secondary reasons for withdrawal.
§§ Statistically significant versus allopurinol ($P \leq 0.05$) and versus febuxostat 120 mg ($P \leq 0.05$).

mg. One of these subjects experienced a severe papular rash that led to discontinuation from the study, and the second subject experienced severe contact dermatitis but continued in the study.

Serious adverse events. There were no deaths reported during the study. Subjects experienced serious AEs with similar frequency in all groups (Table 3). The most frequent serious AEs observed in all treatment groups were cardiovascular disorders (chest pain, coronary artery disease, myocardial infarction, and atrial fibrillation). These subjects each had a history of underlying cardiovascular disease and/or risk factors. Nine of 34 subjects with serious AEs withdrew due to the serious AE (Table 3).

Only 1 subject experienced a serious AE that was considered by the investigator to be related to the study drug. This subject reported a history of kidney stones and experienced a gradual increase in serum creatinine while receiving febuxostat 240 mg (1.1 mg/dl on day 1 to 1.5 mg/dl on the last day of the study, day 197). The serum creatinine level returned to within normal limits (1.3 mg/dl) during treatment with febuxostat 120 mg in a subsequent extension trial.

Adverse events leading to withdrawal. AEs leading at least in part to study discontinuation occurred in 78 subjects with similar frequency across treatments (Table 3). These events were generally mild to moderate in severity, with the most common being abnormal findings on liver function tests (discussed above) and diarrhea. Eight subjects withdrew from the study due to diarrhea: <1% (2 of 267) in the febuxostat 80 mg group, <1% (1 of 269) in the febuxostat 120 mg group, 3% (4 of 134) in the febuxostat 240 mg group, 0% (0 of 134) in the placebo group, and <1% (1 of 268) in the allopurinol group.

Table 4. Liver function test results*

	Placebo (n = 129)	Febuxostat 80 mg (n = 258)	Febuxostat 120 mg (n = 264)	Febuxostat 240 mg (n = 127)	Allopurinol 300 mg (n = 262)
ALT ≥1.5 times the ULN	19 (15)	64 (25)†	57 (22)	24 (19)	52 (20)
AST ≥1.5 times the ULN	14 (11)	49 (19)‡	40 (15)	13 (10)	33 (13)
Concurrent results					
ALT ≥1.5 times the ULN and AST ≥1.5 times the ULN	10 (8)	38 (15)	30 (11)	12 (9)	24 (9)
ALT ≥1.5 times the ULN and total bilirubin ≥2 mg/dl	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)
AST ≥1.5 times the ULN and total bilirubin ≥2 mg/dl	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)
ALT ≥1.5 times the ULN and alk. phos. ≥2 times the ULN	0	1 (<1)	0	0	0
AST ≥1.5 times the ULN and alk. phos. ≥2 times the ULN	0	2 (<1)	0	0	0

* Values are the number (percentage). ALT = alanine aminotransferase; ULN = upper limit of normal; AST = aspartate aminotransferase; alk. phos. = alkaline phosphatase.
† Statistically significant versus placebo ($P < 0.050$).
‡ Statistically significant versus placebo ($P < 0.050$) and versus febuxostat 240 mg ($P < 0.050$).

DISCUSSION

The APEX trial is the largest randomized controlled clinical trial to date comparing febuxostat, allopurinol, and placebo in hyperuricemic subjects with gout. Employing a rigorous primary end point of last 3 monthly serum urate levels <6.0 mg/dl, this 28-week study demonstrated that treatment with febuxostat significantly reduced and maintained serum urate levels <6.0 mg/dl in the majority of subjects, and even in many subjects with a baseline serum urate level >10.0 mg/dl. In contrast, the proportion of subjects responding to allopurinol (22%) was lower than anticipated based on a review of the literature (35–38), but was consistent with the results of a previously reported clinical trial (FACT) (10). Reasons for the limited efficacy of allopurinol in the FACT have previously been discussed (10) and likely include the high mean baseline serum urate levels and the use of fixed rather than titrated doses of allopurinol. Nevertheless, the urate-lowering responses to febuxostat 80 mg, 120 mg, or 240 mg were more robust than the responses to commonly used doses of allopurinol (11), regardless of baseline serum urate level.

The inclusion of subjects with impaired renal function in this clinical trial provides additional clinically relevant insights. In the few subjects with impaired renal function receiving the recommended allopurinol dose (100 mg), end points of serum urate levels <6.0 mg/dl were not achieved. Titration to higher doses of allopurinol might have provided better urate-lowering efficacy as recently reported (39,40); however, there are currently no randomized controlled trials using allopurinol dose titration in patients with gout (7,41).

This study was only 28 weeks in duration and did not demonstrate a difference among treatment groups in reducing gout flare incidence. A 3-year retrospective study by Shoji et al (12) found that reduction of serum urate levels to ≤6.0 mg/dl eventually resulted in a reduced incidence of gout flares. It is likely that differences in flare rates between urate-lowering therapy and placebo may become more distinct with longer-term therapy, but documentation in longer studies is needed.

The occurrence rate for any AE was similar across treatment groups. Incidences of diarrhea and dizziness were significantly more frequently reported in the febuxostat 240 mg group. No other events showed any stepwise increase in rates with higher doses of febuxostat. Entry criteria limited participation to subjects with no more than 14 alcoholic beverages per week. In practice, it will be important for physicians to follow possible liver function effects in heavier drinkers.

Serious AEs were reported with similar frequencies in all groups, the most common of which were cardiovascular disorders. These subjects each had documented underlying cardiovascular disease and/or risk factors. As might have been expected, withdrawals due to gout flares were more common in the febuxostat groups, possibly due to urate crystal mobilization with more abrupt lowering of serum urate with febuxostat compared with allopurinol. Antiinflammatory prophylaxis may need to be studied further and may need to be continued longer than 8 weeks when using potent urate-lowering agents. In addition, there is a need to educate patients to be aware of acute flares and seek prompt treatment.

Limitations to this large and complex study are those observed in hindsight. Fewer subjects with renal impairment were enrolled than anticipated. Additional clinical trials are needed to provide guidance on how to best achieve target serum urate levels in patients with impaired renal function, including those with more severe renal impairment, as will likely be seen in practice. In addition, accurate measurement of tophi continues to be problematic in the clinical setting and highlights the need for a more reliable measure so that the effects of urate-lowering therapy can be adequately assessed. Likewise, criteria for the diagnosis and management of acute gout flares need to

be more clearly defined so that flares can be more reproducibly described and quantified.

The results of the current study demonstrate that treatment with febuxostat 80 mg, 120 mg, and 240 mg for 28 weeks effectively reduces serum urate levels in subjects with hyperuricemia and gout and that these effects are significantly greater than those produced by the commonly used doses of up to 300 mg of allopurinol or by placebo. The efficacy of febuxostat in subjects with renal impairment is promising and warrants further study.

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AUTHOR CONTRIBUTIONS

Dr. Schumacher had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Schumacher, Becker, Wortmann, MacDonald, Hunt, Streit, Joseph-Ridge.

Acquisition of data. Becker, MacDonald, Streit, Lademacher.

Analysis and interpretation of data. Schumacher, Becker, Wortmann, MacDonald, Hunt, Streit, Lademacher, Joseph-Ridge.

Manuscript preparation. Schumacher, Becker, Wortmann, MacDonald, Hunt, Streit, Lademacher, Joseph-Ridge, Joyce N. Riffin (nonauthor; Takeda Pharmaceuticals, Inc., Deerfield, IL).

Statistical analysis. Hunt, Lademacher.

ROLE OF THE STUDY SPONSOR

The study was designed by the academic authors and the corporate sponsor, Takeda Global Research & Development Center, Inc. Representatives of Takeda Global Research & Development Center, Inc., collected the data and statisticians at Takeda Global Research & Development Center, Inc., conducted all statistical analyses. All authors had access to the data and vouch for the veracity and completeness of the data and data analysis.

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