Clinical Efficacy and Safety of Successful Longterm Urate Lowering with Febuxostat or Allopurinol in Subjects with Gout

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ABSTRACT. ***Objective.*** To determine longterm urate-lowering efficacy and clinical benefits and safety of therapy with febuxostat or allopurinol in subjects with gout.

Methods. Subjects (n = 1086) in this open-label extension study were assigned to fixed-dose daily urate-lowering treatment (ULT) with febuxostat (80 mg or 120 mg) or allopurinol (300 mg). ULT reassignment was permitted during months 1 to 6 to achieve serum urate (SUA) concentrations between 3.0 and < 6.0 mg/dl. Flares requiring treatment, tophus size, safety, and SUA levels were monitored during up to 40 months of ULT maintenance.

Results. After 1 month initial treatment, > 80% of subjects receiving either febuxostat dose, but only 46% of subjects receiving allopurinol, achieved SUA < 6.0 mg/dl. After ULT reassignment, > 80% of all remaining subjects maintained the primary efficacy endpoint of SUA < 6.0 mg/dl at each visit. More subjects initially randomized to allopurinol required ULT reassignment to achieve SUA < 6.0 mg/dl compared with subjects receiving febuxostat. Maintenance of SUA < 6.0 mg/dl resulted in progressive reduction to nearly 0 in proportion of subjects requiring gout flare treatment. Baseline tophus resolution was achieved by 46%, 36%, and 29% of subjects maintained on febuxostat 80 mg, febuxostat 120 mg, and allopurinol, respectively. Overall adverse event rates (including cardiovascular adverse event rates), adjusted for 10-fold greater febuxostat than allopurinol exposure, did not differ significantly among treatment groups.

Conclusion. Durable maintenance of goal range SUA level with either dose of febuxostat or in smaller numbers of subjects with allopurinol resulted in near elimination of gout flares and improved tophus status over time. Registered as NCT00175019. (J Rheumatol First Release March 15 2009; doi:10.3899/jrheum.080814)

Key Indexing Terms:
GOUT HYPERURICEMIA FEBUXOSTAT ALLOPURINOL SERUM URATE

Hyperuricemia, defined as serum urate (SUA) concentrations at or above the limit of urate solubility in serum (approximately 6.8 mg/dl), is a common biochemical aberration and is often manifested clinically as the urate crystal deposition disease, gout[1]. The management of chronic gout is directed at lowering and maintaining SUA at subsaturating levels, most often < 6.0 mg/dl. Achievement of this goal usually requires urate-lowering pharmacotherapy (ULT), which, when successful, often results in reduction in the incidence of acute gout flares and resolution of tophi[2-8].

The most commonly employed approach to ULT is reduction of uric acid production using the purine analog xanthine-oxidase (XO) inhibitor allopurinol[9]. Although approved by the US Food and Drug Administration (FDA) in a dose range from 100 mg to 800 mg daily, allopurinol is commonly dosed at 100 mg to 300 mg daily[3,5,10,11]. Limitations of allopurinol therapy include failure to achieve target SUA at commonly utilized doses; rashes; and rare, but frequently fatal, allopurinol hypersensitivity syndrome (AHS)[11,12]. Moreover, reduction of allopurinol dose has been recommended for patients with chronic renal functional impairment[10], but there are no clinical trials confirming that dose reduction limits the risks of severe allopurinol toxicity[13], and downward dose adjustment frequently results in failure to achieve the urate-lowering goal range[11].

The only currently available alternative ULT strategy is

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increasing renal uric acid excretion with a uricosuric agent, such as probenecid or benzbromarone. However, the latter agent is not approved in the United States and many other countries, and probenecid requires multiple daily dosing and is limited in effectiveness in patients with impaired renal function[1,3]. A third approach to ULT, conversion of urate to allantoin by administration of recombinant uricase, is currently in development for management of severe gout that has been refractory to currently available agents[1].

Febuxostat, a selective inhibitor of XO that is not a purine analog and is metabolized mainly in the liver[14], is in late-stage development for the management of hyperuricemia in patients with gout. Recently, 2 randomized, double-blind Phase III trials evaluating the efficacy and safety of febuxostat (80 mg and 120 mg) in reducing SUA levels to < 6.0 mg/dl compared with allopurinol 300 mg and/or placebo have been reported[15,16]. The urate-lowering efficacy of febuxostat, 80 mg and 120 mg, was superior to that of placebo and allopurinol 300 mg in a 28-week trial[16] and to that of allopurinol 300 mg in a 1-year trial[15]. Additionally, febuxostat dose reduction appears to be unnecessary in mild to moderate renal impairment[17]. Although the results of the Phase III trials suggested that successful maintenance of goal-defined urate-lowering might result in decreased flare incidence and tophus size reduction, definitive longterm clinical efficacy and safety data were not obtained within the treatment periods of these trials.

In order to evaluate longterm clinical efficacy and safety of febuxostat at 80 mg and 120 mg daily and allopurinol 300 mg daily, an open-label extension of the 2 Phase III febuxostat and allopurinol comparative trials was undertaken. We report the results of an extended treatment trial, fEbuXostat/allopurinol Comparative Extension Long-term study (EXCEL), in subjects achieving SUA < 6.0 mg/dl during treatment with febuxostat or allopurinol for up to 40 months.

MATERIALS AND METHODS

Study design. At each of the 174 participating sites in the US and Canada, the Investigator's Brochure, all protocols and protocol amendments, informed consent/privacy authorization forms (the Health Insurance Portability and Accountability Act form in the US and the Personal Information Protection and Electronic Documents Act form in Canada), and subject information forms were approved by an institutional review board or an independent ethics committee. Registered as NCT00175019.

The 1280 subjects who previously completed one of the 2 Phase III double-blind trials[15,16] were invited to enroll in the current study. All 1086 subjects who volunteered for the study met criteria for the diagnosis of gout according to the preliminary criteria of the American Rheumatism Association[18]. Exclusion criteria (previously described[15,16]) included pregnancy or lactation; serious drug-related adverse event (AE) in the prior study; other significant medical conditions that would interfere with treatment safety or compliance; or known intolerance to allopurinol. All participating subjects signed informed consent/privacy authorization forms.

Subjects (n = 351) enrolled under the original study protocol initially received febuxostat 80 mg once daily. During the first 6 months of treatment, these subjects could switch their febuxostat dose to febuxostat 120 mg if SUA was ≥ 6.0 mg/dl. Subjects titrated to febuxostat 120 mg could switch back to febuxostat 80 mg, if necessary, to maintain SUA within the target range (≥ 3.0 and < 6.0 mg/dl) or in response to an AE.

In response to an FDA request for inclusion of an allopurinol treatment arm in our study, the additional 735 subjects were enrolled under an amended protocol and randomly assigned in a 2:2:1 ratio to receive febuxostat 80 mg, febuxostat 120 mg, or allopurinol (Zyloprim; Par Pharmaceutical, Woodcliff Lake, NJ, USA) 300 or 100 mg daily. Assignment to an allopurinol dose was determined by renal function; subjects with serum creatinine (sCr) ≤ 1.5 mg/dl received 300 mg daily; those with initial sCr > 1.5 mg/dl and ≤ 2.0 mg/dl received 100 mg daily.

Eight subjects received allopurinol 100 mg for a limited time; 7 switched to allopurinol 300 mg or febuxostat, and 1 subject prematurely discontinued the study. As such, data for all subjects receiving either dose of allopurinol are analyzed and reported together as "allopurinol."

Subjects were required to be receiving a stable daily maintenance dose of ULT, appropriate for the respective protocol under which they enrolled, by the end of month 6 of the trial. Subjects with 3 consecutive SUA > 6.0 mg/dl were to be withdrawn from the study as therapeutic failures unless out of target range SUA values were determined by the investigator to be due to a change in diet or medication, alcohol consumption, or incomplete compliance with treatment.

During the first 2 months in the study, subjects were provided with either naproxen (250 mg twice daily; Roche Pharmaceuticals, Nutley, NJ, USA) or colchicine (0.6 mg daily; West-Ward Pharmaceutical Corporation, Eatontown, NJ, USA) to reduce the risk of gout flares. Choice of prophylactic antiinflammation treatment was determined by the investigator based upon sensitivity or intolerance to either drug; subjects with sCr > 1.5 mg/dl usually received colchicine. Subjects who experienced gout flares during prophylactic therapy were asked to take an additional dose of their ongoing prophylactic medication for 1 or 2 days. If this proved insufficient to treat a flare during the prophylaxis period and for the remainder of the study, gout flares were treated with nonsteroidal antiinflammatory drugs, analgesics, corticosteroids, or colchicine, at investigator discretion. Gout flares were not considered AE and were recorded separately.

Physical examination and assessments of SUA, gout flares, number and size of palpable tophi, laboratory tests, AE, and concomitant medications were performed every 2 months and at the final visit. Trained personnel used a physical method to measure selected tophi as described[19], and an index tophus of at least 1 cm × 1 cm area was identified for serial assessment in each patient with such nodules.

Efficacy variables. The primary efficacy variable, the proportion of subjects with SUA < 6.0 mg/dl, was evaluated at each visit. Secondary efficacy variables included percentage reduction from baseline SUA; proportion of subjects with SUA decreasing to < 6.0 mg/dl across treatment changes; reduction in the incidence of gout flares requiring treatment; percentage reduction in number of tophi in subjects with such nodules; and reduction in the size or disappearance of the index tophus.

Statistical methods. All statistical tests were 2-sided at the 0.05 significance level and were performed using SAS v9.1.3 (SAS Institute Inc., Cary, NC, USA) on the UNIX operating system. All subjects who received at least 1 dose of study drug were included in both efficacy and safety analyses. Demographic and baseline variables were determined from data collected at enrollment into the respective Phase III trials that each subject completed prior to enrollment in this extension study[15,16].

Efficacy variables specifically comparing SUA in response to febuxostat (at either dose) and allopurinol are reported by initial treatment, which summarizes subjects by drug and/or dose to which the subject was initially assigned. Responses of SUA to ULT after the period of permitted drug and/or dose changes (months 1 through 6) are reported by final (maintenance) treatment group because in this later phase of the trial the major aim was to assess durability of urate-lowering and clinical efficacy at ULT doses previously established as effective in achieving the goal urate range in each subject. Gout flares and tophus changes are summarized by the

maintenance treatment each subject was receiving. AE are reported by treatment at observation, which summarizes subjects by the treatment they were receiving at the time of occurrence of the respective AE.

RESULTS

Subject demographics and disposition. In total, 1086 subjects who previously completed either the 28-week[16] or the 52-week[15] Phase III study enrolled in this extension study (351 subjects under the original protocol and 735 after the protocol was amended to include allopurinol; Figure 1). Subjects were considered to have completed the study if they completed a visit on or after November 1, 2006, when study dosing was concluded. As such, 664 subjects completed the study, with duration of treatment ranging from 31 to 40 months. The majority of subjects were male, Caucasian, and in the age range of 45 to 65 years. Most subjects were obese [body mass index (BMI) ≥ 30 kg/m^2; Table 1].

Unless otherwise specified, "baseline" was defined at entry into either previous Phase III trial[15,16]. Mean baseline

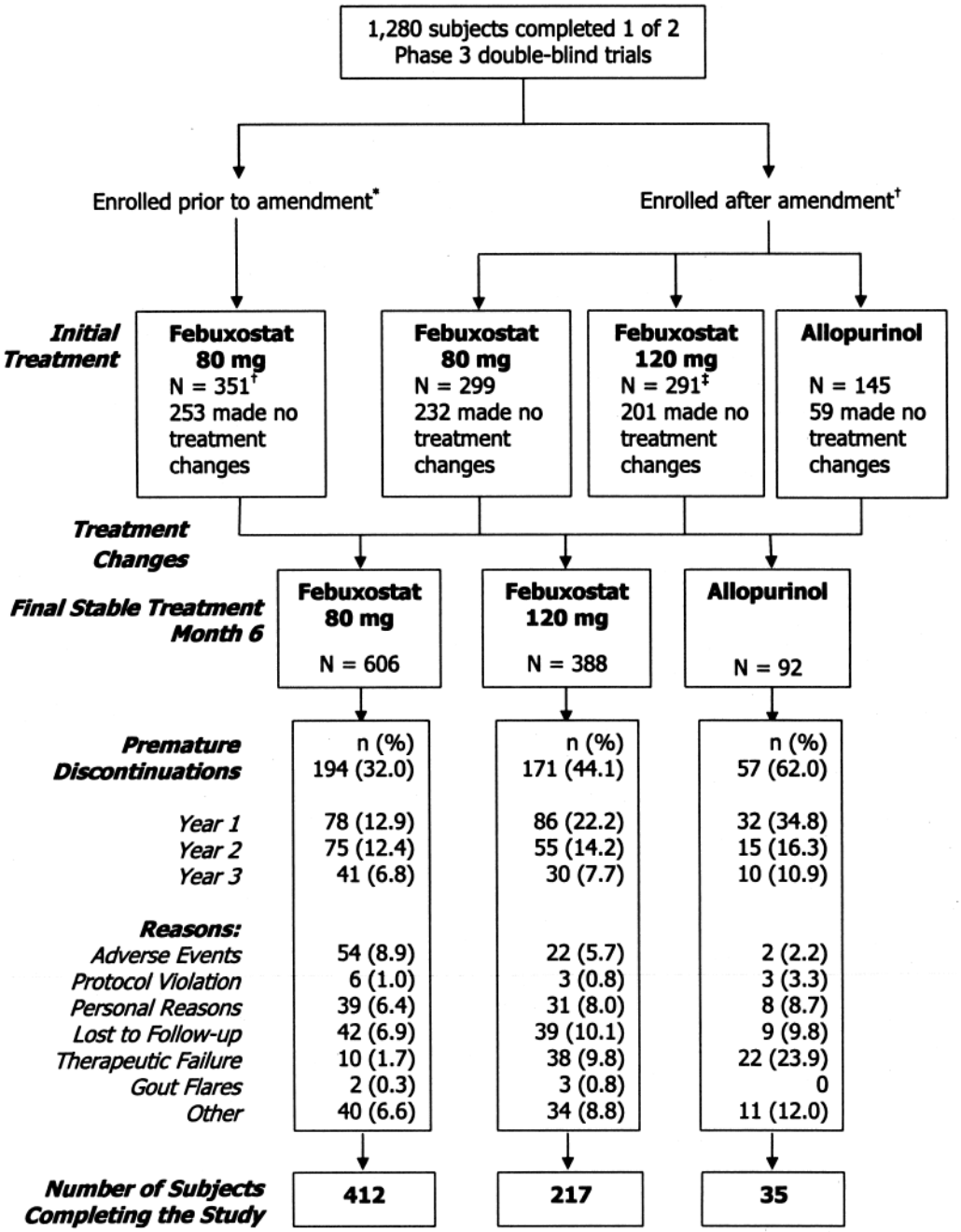


Figure 1. Flow of subjects through the trial. *Subjects could change treatments between febuxostat 80 mg and 120 mg through month 6. †Subjects could change treatments between febuxostat 80 or 120 mg or allopurinol through month 6. ‡One subject assigned to febuxostat 80 mg under initial protocol briefly received febuxostat 120 mg due to investigator error.

Table 1. Subjects' demographic data by initial treatment.

Variable	Febuxostat 80 mg, N = 649	Febuxostat 120 mg, N = 292	Allopurinol, N = 145
Serum urate (mg/dl), n (%)			
< 9.0	183 (28.2)	97 (33.2)	36 (24.8)
9.0 to < 10.0	219 (33.7)	90 (30.8)	54 (37.2)
≥ 10.0	247 (38.1)	105 (36.0)	55 (37.9)
Mean ± SD	9.83 ± 1.253	9.74 ± 1.281	9.82 ± 1.157
Renal function, n (%)			
Normal	636 (98.0)	286 (97.9)	144 (99.3)
Impaired*	13 (2.0)	6 (2.1)	1 (0.7)
Medical history, n (%)			
Cardiovascular disease	71 (10.9)	33 (11.3)	14 (9.7)
Congestive heart failure	11 (1.7)	8 (2.7)	0
Diabetes	46 (7.1)	15 (5.1)	12 (8.3)
Hypercholesterolemia	48 (7.4)	16 (5.5)	9 (6.2)
Hyperlipidemia	229 (35.3)	89 (30.5)	47 (32.4)
Hypertension	295 (45.5)	115 (39.4)	73 (50.3)
Alcohol use, n (%)			
Drinker†	433 (66.74)	197 (67.5)	105 (72.4)
Non-/Ex-drinker	216 (33.3)	95 (32.5)	40 (27.6)
Race, n (%)			
Asian	19 (2.9)	4 (1.4)	5 (3.4)
Black or African American	51 (7.9)	30 (10.3)	15 (10.3)
White	519 (80.0)	233 (79.8)	110 (75.9)
Hispanic or Latino	40 (6.2)	15 (5.1)	11 (7.6)
Other	20 (3.1)	10 (3.4)	4 (2.8)
Age, yrs, n (%)			
< 45	192 (29.6)	86 (29.5)	45 (31.0)
45 to 65	373 (57.5)	178 (61.0)	89 (61.4)
> 65	84 (12.9)	28 (9.6)	11 (7.6)
Mean ± SD	51.4 ± 11.95	50.9 ± 11.57	51.0 ± 11.30
Range	24–84	24–84	29–83
Weight, lb			
Mean ± SD	223.3 ± 43.01	230.3 ± 47.87	234.7 ± 49.69
Range	123–390	135–399	136–468
BMI, kg/m^2, n (%)			
< 18.5	0	0	0
18.5 to < 25	40 (6.2)	10 (3.4)	6 (4.1)
25 to < 30	215 (33.1)	92 (31.5)	42 (29.0)
≥ 30	394 (60.7)	189 (64.7)	97 (66.9)
Missing	0	1 (0.3)	0
Mean ± SD	32.3 ± 5.78	33.2 ± 6.17	33.8 ± 6.79
Range	21–61	22–59	21–65
Height, in			
Mean ± SD	69.7 ± 3.24	69.8 ± 3.18	69.9 ± 3.32
Range	59–80	61–78	59–79

* Defined as serum creatinine > 1.5 mg/dl. † 1–14 drinks/wk.

SUA for all subjects was 9.81 mg/dl; subjects were to have SUA ≥ 8.0 mg/dl. At baseline, 214 subjects (20%) had at least 1 palpable tophus. Normal renal function, as defined by sCr ≤ 1.5 mg/dl, was identified in the great majority of subjects (1066/1086; 98%). Comorbid conditions were common. The most frequent medical conditions were hypertension (44%) and hyperlipidemia (34%) (Table 1). Alcohol consumption (defined as 1 to 14 drinks imbibed weekly) was reported by 68% of subjects. Concomitant medication was taken by 95% of subjects during the study. The most common concomitant medications used during the study were antiinflammatory and antirheumatic products (57%), analgesics (46%), antibiotics (39%), and antihyperlipidemia agents (38%). Although some of the antihypertensive and antihyperlipidemia medications used are known to influence SUA[3], a systematic influence on the overall efficacy analysis is unlikely.

Under the initial protocol for our study, 351 subjects were assigned to receive febuxostat 80 mg daily (1 subject received febuxostat 120 mg due to investigator error).

Among 735 subjects enrolled under the amended protocol, 299 initially received febuxostat 80 mg, 291 received febuxostat 120 mg, and 145 received allopurinol daily.

Overall, 422 of 1086 subjects discontinued treatment prematurely: 196, 145, and 81 subjects, respectively, during years 1, 2, and 3 (Figure 1). Primary reasons for discontinuation were reported as "lost to followup" (90/1086; 8.3%); "personal reasons" (78/1086; 7.2%); AE (78/1086; 7.2%); and treatment failure (70/1086; 6.4%). Study drug compliance (evaluated by residual tablet count at each visit) was similar across all treatments; mean percentage compliance by initial treatment was 94.9%, 95.2%, and 95.1% in subjects taking febuxostat 80 mg, febuxostat 120 mg, and allopurinol, respectively.

Among all subjects, 341/1086 subjects (31%) had at least 1 change in ULT (Figure 1). Of 351 subjects enrolled under the initial protocol, 253 (72%) did not change treatment, while 98 (28%) subjects made at least 1 change. Sixty-seven percent (492/735) of subjects enrolled under the amended protocol remained on their initial treatment, while 243 (33%) made at least 1 treatment change. Failure to achieve SUA < 6.0 mg/dl on initial ULT resulted in treatment change in 22%, 8%, and 57% of subjects initially receiving febuxostat 80 mg, febuxostat 120 mg, and allopurinol, respectively (Table 2).

Of 649 subjects initially treated with febuxostat 80 mg, 606 received febuxostat 80 mg as maintenance ULT. In contrast, the number of patients receiving febuxostat 120 mg increased from 292 initially assigned this dose to 388 maintained. Finally, 145 subjects initially received allopurinol, but only 92 subjects were maintained with allopurinol.

Primary efficacy endpoint. After 1 month of initial treatment, 81% (501/620) and 87% (241/277) of subjects receiving 80 mg and 120 mg febuxostat, respectively, had SUA < 6.0 mg/dl. For the duration of treatment, the percentages of subjects maintaining SUA < 6.0 mg/dl on these doses of febuxostat remained above 80%. Among subjects initially receiving allopurinol, only 46% (64/139) achieved SUA < 6.0 mg/dl in the first month, but, as subjects failing to meet this goal urate range were shifted to febuxostat therapy, the percentage maintaining goal range on allopurinol 300 mg rose to 82% by month 12 (37/45). Between month 12 and the termination of the study, goal range SUA was maintained by 75% to 100% of subjects remaining in each study group at each visit (Figure 2).

Secondary efficacy endpoints. Mean percentage reductions from baseline SUA, analyzed at the last visit on initial treatment, were 47%, 53%, and 32% for febuxostat 80 mg, febuxostat 120 mg, and allopurinol, respectively.

For subjects who changed treatments as a result of failure to achieve SUA < 6.0 mg/dl on initial treatment, response to subsequent treatments varied. Of 102 subjects who did not achieve SUA < 6.0 mg/dl on febuxostat 80 mg, 62 (61%) achieved SUA < 6.0 mg/dl after switching to febuxostat 120 mg. Of 24 subjects who did not respond to a febuxostat dose of either 80 mg or 120 mg, 4 (17%) who were switched to allopurinol 300 mg achieved SUA < 6.0 mg/dl. Finally, of 78 subjects who did not achieve SUA < 6.0 mg/dl with allopurinol, 41% (32/78) did so during subsequent treatment with febuxostat 80 mg, and an additional 23% (18/78) did so in response to treatment with febuxostat 120 mg.

The incidences of gout flares requiring treatment are shown in Figure 3 for subjects in each ULT maintenance group. As previously reported[15], gout flare rates increased sharply in the period immediately after prophylaxis withdrawal (the end of week 8), but flare rates subsequently decreased over time for all treatment groups. As goal urate levels were maintained in > 80% of subjects in the entire remaining treatment population at each visit, gout flare was reported in < 4% of subjects after 18 months of ULT.

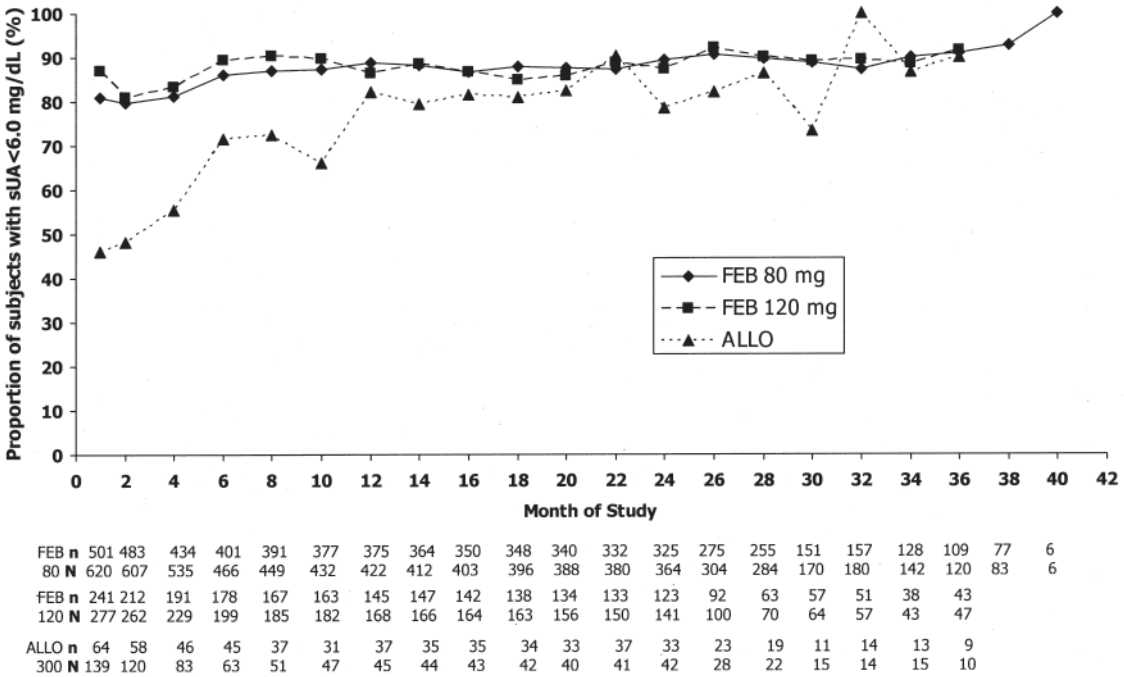
Figure 4 summarizes a comparison of tophus findings at baseline and at the final study visit. Among subjects with tophi, longterm maintenance of the goal SUA range was accompanied by reductions in the areas of index tophi and in the number of tophi and by the proportion of index tophi undergoing complete resolution.

Adverse events. AE were summarized according to the treatment subjects were receiving at the time of the events; consequently, subjects could be included in more than 1 treatment. Total duration of exposure was 1480 patient-years (PY) for febuxostat 80 mg, 803 PY for febuxostat 120 mg, and 173 PY for allopurinol. That is, exposure to febuxostat

Table 2. Reasons for reassignment of urate-lowering therapy from initial treatment.

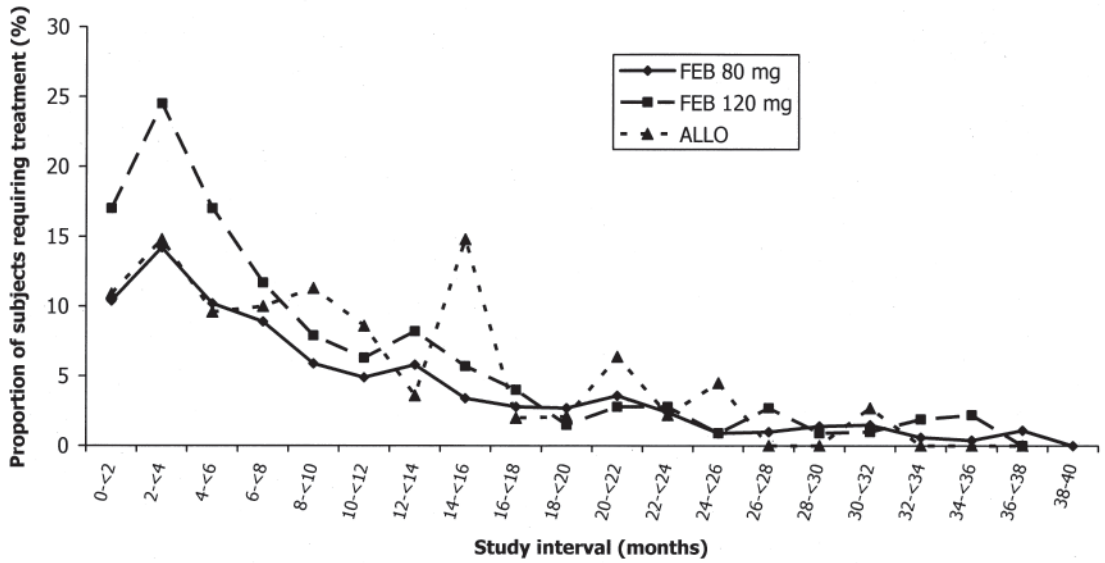
Reason	Febuxostat 80 mg, N = 649 n (%)	Febuxostat 120 mg, N = 292 n (%)	Allopurinol, N = 145 n (%)
Overall	164 (25.2)	91 (31.2)	86 (59.3)
SUA > 6.0 mg/dl	141 (21.7)	22 (7.5)	82 (56.6)
SUA < 3.0 mg/dl	1 (0.2)	41 (14.0)	0
Adverse event	1 (0.2)	7 (2.4)	1 (0.7)
Other	18 (2.8)	20 (6.8)	3 (2.1)
No reason provided	3 (0.5)	1 (0.3)	0

SUA: serum uric acid.



FEB 80	n	501	483	434	401	391	377	375	364	350	348	340	332	325	275	255	151	157	128	109	77	6
	N	620	607	535	466	449	432	422	412	403	396	388	380	364	304	284	170	180	142	120	83	6
FEB 120	n	241	212	191	178	167	163	145	147	142	138	134	133	123	92	63	57	51	38	43		
	N	277	262	229	199	185	182	168	166	164	163	156	150	141	100	70	64	57	43	47		
ALLO 300	n	64	58	46	45	37	31	37	35	35	34	33	37	33	23	19	11	14	13	9		
	N	139	120	83	63	51	47	45	44	43	42	40	41	42	28	22	15	14	15	10		

Figure 2. Proportion of subjects receiving initial urate-lowering agent who achieved/maintained SUA < 6.0 mg/dl. n: number of subjects with SUA < 6.0 mg/dl; N: total number of subjects on initial treatment; FEB: febuxostat; ALLO: allopurinol.



FEB 80	n	63	82	58	49	32	26	30	17	14	13	17	11	4	5	6	6	2	1	2	0
	N	606	579	566	552	540	527	516	507	492	483	472	458	439	430	417	392	356	269	170	32
FEB 120	n	66	90	59	39	25	19	24	16	11	4	7	7	2	6	2	2	3	2	0	
	N	388	367	347	332	316	302	293	282	272	266	252	246	234	220	213	193	159	91	10	
ALLO 300	n	10	12	7	7	7	5	2	8	1	1	3	1	2	0	0	1	0	0	0	
	N	92	81	73	70	62	58	56	54	50	48	47	46	44	41	39	37	29	20	1	

Figure 3. Incidence of gout flares requiring treatment in each study interval, by maintenance treatment. n: number of subjects requiring flare treatment; N: total number of subjects on specified final stable treatment at that timepoint; FEB: febuxostat; ALLO: allopurinol.

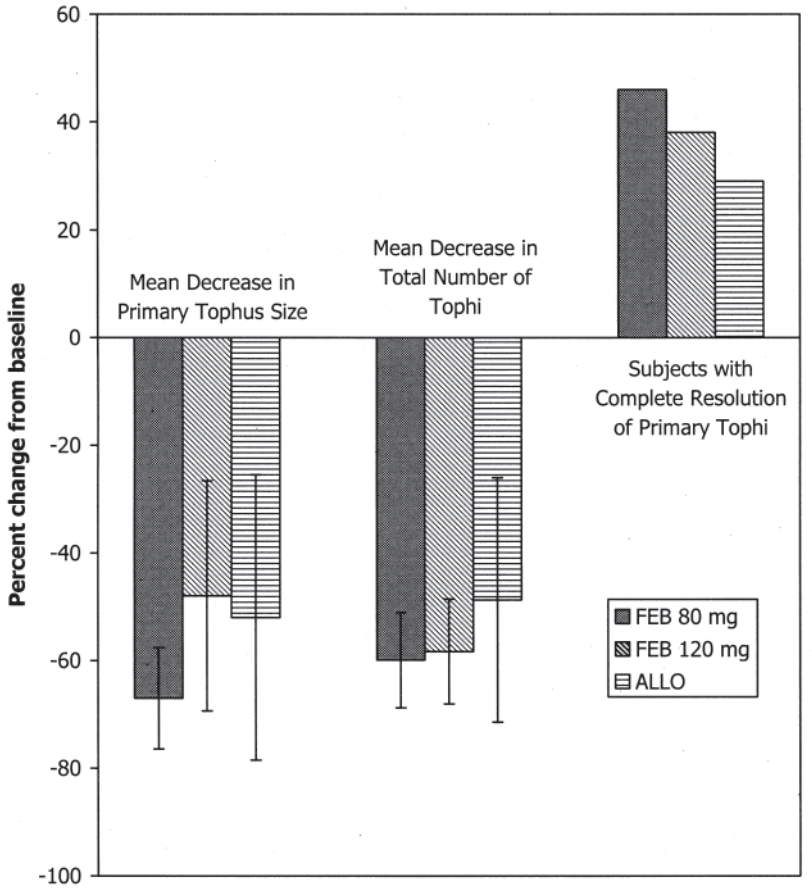


Figure 4. Tophus status at final visit compared with baseline. Error bar represents 2 times standard error. FEB: febuxostat; ALLO: allopurinol.

80 mg and 120 mg was 8.6 and 4.6 times greater, respectively, than exposure to allopurinol.

When adjusted for duration of exposure, total AE were reported at rates of 227, 216, and 245 events per 100 PY of exposure for subjects receiving febuxostat 80 mg, febuxostat 120 mg, and allopurinol, respectively. Table 3 shows the most frequently reported AE (≥ 5 events per 100 PY of exposure) by treatment. Statistically significant mean increases from baseline for aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were observed for all 3 treatments. Overall, the mean increases in liver function tests of AST and ALT observed from baseline to final visit in any of the 3 treatments were small (1.8 to 4.8 U/l of ALT and 2.2 to 4.0 U/l for AST). Investigators designated liver function analyses abnormalities as reasons for withdrawing subjects in 9, 4, and 2 subjects in the febuxostat 80 mg, 120 mg, and allopurinol treatment groups, respectively. There were no set thresholds for withdrawals. The majority of laboratory elevations were transient and were ≤ 3 times the upper limit of normal. Two subjects receiving febuxostat 80 mg had > 10 times the upper limit of normal ALT/AST, with concurrent bilirubin > 2 times the upper limit of normal: 1 subject with a bile duct stone (value returned to baseline in 10 days) and one other with fatal bile duct cancer.

Serious AE (SAE) were reported by 161 subjects. Rates of SAE were 11, 9, and 12 events per 100 PY of exposure for febuxostat 80 mg, febuxostat 120 mg, and allopurinol, respectively. Cardiac disorders were the most frequently reported SAE. Comparable rates of SAE cardiac disorders were observed across treatments, whether reported by percentage of subjects (4%, 2%, and 3%, for febuxostat 80 mg, febuxostat 120 mg, and allopurinol, respectively) or when adjusted for exposure (Table 3). A total of 48 subjects reported SAE cardiac disorders. All subjects who reported cardiac events had a history of cardiovascular disease and/or other underlying risk factors (e.g., BMI ≥ 30 kg/m^2, hypertension, hyperlipidemia). Investigators did not consider any of the cardiac SAE to be related to treatment.

Ten subjects died during the study (7 receiving febuxostat 80 mg and 3 receiving febuxostat 120 mg). Six deaths were attributed to cardiovascular events; all occurred in subjects with extensive histories of cardiovascular disease. Two deaths were due to cancer; 1 was due to a bleeding event in

Table 3. Adverse events. Data are number of events (rate per patient-year).

	Febuxostat 80 mg, N = 801 PY = 1480	Febuxostat 120 mg, N = 487 PY = 803	Allopurinol, N = 178 PY = 173
Most frequently reported* adverse events**			
Total number of adverse events	3362 (227)	1736 (216)	423 (245)
Upper respiratory tract infections	375 (25)	181 (23)	38 (22)
Musculoskeletal and connective tissue signs and symptoms	197 (13)	116 (14)	31 (18)
Joint-related signs and symptoms	134 (9)	72 (9)	14 (8)
Skin injuries	31 (2)	11 (1)	9 (5)
Headaches	58 (4)	64 (8)	10 (6)
Lower respiratory tract and lung infections	81 (5)	31 (4)	7 (4)
Vascular hypertensive disorders	81 (5)	31 (4)	7 (4)
Gastrointestinal atonic and hypomotility disorders	25 (2)	23 (2)	9 (5)
Diarrhea	40 (3)	37 (5)	4 (2)
All serious adverse events†			
Total number of serious adverse events	165 (11)	73 (9)	21 (12)
Cardiac disorders	46 (3)	17 (2)	5 (3)
Musculoskeletal and connective tissue disorders	8 (< 1)	11 (1)	2 (1)
Infections and infestations	28 (2)	7 (< 1)	3 (2)
Nervous system disorders	12 (< 1)	6 (< 1)	2 (1)
Gastrointestinal disorders	5 (< 1)	8 (< 1)	2 (1)
Hepatobiliary disorders	10 (< 1)	1 (< 1)	3 (2)
Vascular disorders	10 (< 1)	4 (< 1)	2 (1)
Metabolism and nutrition disorders	2 (< 1)	2 (< 1)	0
Renal and urinary disorders	4 (< 1)	2 (< 1)	0
Respiratory, thoracic, and mediastinal disorders	10 (< 1)	2 (< 1)	1 (< 1)
Injury, poisoning, and procedural complications	13 (< 1)	1 (< 1)	0
Neoplasms benign, malignant, and unspecified	11 (< 1)	5 (< 1)	0
Ear and labyrinth disorders	0	4 (< 1)	0
Blood and lymphatic system disorders	2 (< 1)	0	0
General disorders and administration site conditions	2 (< 1)	2 (< 1)	0
Skin and subcutaneous tissue disorders	1 (< 1)	0	1 (< 1)
Congenital, familial, and genetic disorders	0	1 (< 1)	0
Investigations	1 (< 1)	0	0
Deaths	7 (< 1)	3 (< 1)	0

* Reported by MedDRA high-level term; ** ≥ 5 events per 100 PY; † reported by system organ class. PY: Patient-years.

a subject with angina and chronic obstructive pulmonary disease who was receiving warfarin and heparin; and 1 was due to postsurgical sepsis. Four subjects who died were ≥ 75 years of age at baseline, 2 were between 65 and 74 years of age, and 4 subjects were ≤ 65 years of age. None of the deaths were assessed by the respective investigators to be related to study drug, and there was no apparent relationship between drug dose or length of drug exposure and death. Deaths occurred between 12 and 964 days after subjects entered the study, and 6 of 10 deaths occurred 30 or more days after last exposure. Mortality rates per 100 PY (95% confidence interval), adjusted for duration of exposure, were 0.47 (0.190–1.975) for febuxostat 80 mg, 0.37 (0.077–1.091) for febuxostat 120 mg, and 0.00 (0.000–2.317) for allopurinol.

During the study, 78 subjects discontinued prematurely due, at least in part, to AE. Rates of AE that led to premature discontinuation, adjusted for exposure, were 5.0, 3.1, and 3.5 events per 100 PY for febuxostat 80 mg, febuxostat 120 mg, and allopurinol, respectively. The most frequently reported AE for discontinuation by percentage of subjects was neoplasia (1% for both febuxostat doses; 0% for allopurinol). Reported neoplasias varied, and included benign neoplasia, B-cell lymphoma, bile duct cancer, prostate cancer, breast cancer, colon cancer, renal cell cancer, small-cell lung cancer, pancreatic cancer, and esophageal cancer.

DISCUSSION

Although a greater proportion of subjects initially randomized to allopurinol than to febuxostat required change in ULT in order to achieve SUA < 6.0 mg/dl, longterm maintenance of SUA in this goal range with either urate-lowering agent was associated with clinical benefits in the form of near elimination of gout flares and considerable reversal of tophus burden over time (Figures 3 and 4). These findings are in accord with those of the double-blind trials in which

the subjects in the current extension study had previously participated[15,16]. The preceding trials also demonstrated superior urate-lowering efficacy for febuxostat at 80 mg or 120 mg compared with that of allopurinol 300 mg, but failed to distinguish between these urate-lowering agents in reductions in the incidence of gout flares or in the size of tophi[15,16]. In the 12-month febuxostat-allopurinol comparative trial[15], however, post-hoc analysis of the incidence of gout flares related to average post-baseline SUA achieved on treatment with either febuxostat or allopurinol demonstrated a reduction in gout flare rates in subjects with average post-baseline SUA < 6.0 mg/dl compared with subjects not reaching this goal urate range. Statistical significance of this difference in flare rates according to maintained urate levels did not, however, emerge until the final 4 weeks of the 52-week treatment period[15], emphasizing the difficulty in demonstrating flare reduction benefits of even successful XO inhibitor-based urate-lowering (much less distinguishing between active agents of this class) in the context of trials of even 1-year duration. The current extension study aimed at maintaining all subjects at SUA < 6.0 mg/dl for up to 3 years, and success in this effort was associated with a continuing reduction in the incidence of gout flares to nearly 0.

With regard to reduction in size and number of tophi, no significant differences were demonstrated in the prior 52-week trial[15] between subjects in the SUA < 6.0 mg/dl and the SUA > 6.0 mg/dl subgroups, despite moderate reduction in tophus size in both subgroups. In the current extension trial, evidence for reduction in tophus burden was demonstrable in each of the 3 ULT maintenance groups after 3 years of successful treatment: complete resolution of an index tophus occurred in approximately 30% to 45% of subjects in the 3 groups, and mean percentage reductions in the size and total number of tophi ranged from approximately 50% to 60%. Although the absence of a control group of untreated or partially treated gout patients with tophi precludes a direct confirmation of a causal relationship between successful ULT and reduced tophus burden, prior investigation[8] has documented an inverse relationship between rates of tophus dissolution and serum urate concentrations maintained in the subsaturating range. Thus, our findings support the view that relief from this manifestation of chronic gout can be achieved with longterm ULT aimed at maintaining SUA in a subsaturating range (< 6.0 mg/dl).

Overall, the results of this large study are compatible with the concept that the achievement and maintenance of subsaturating urate levels is the major determinant of success in resolving the clinical manifestations of gout. Distinctions among urate-lowering agents in clinical practice are likely to depend on the efficacy of urate-lowering possible within the context of safety in dosing.

Some additional information can be derived from examining rates of and reasons for treatment reassignment. Within initial treatment groups, subjects receiving allopurinol experienced the greatest proportion of treatment changes, primarily due to a failure to achieve SUA < 6.0 mg/dl, suggesting inadequacy of allopurinol at a dose of 300 mg in many of these subjects. In several prior studies[15,16,20], the majority of the contemporary population of gout patients with baseline SUA > 8.0 mg/dl do not achieve the SUA goal range specified in our study when receiving this commonly prescribed dose of allopurinol. Interestingly, among subjects switching from allopurinol to one or the other dose of febuxostat, greater than 60% achieved SUA < 6.0 mg/dl. Conversely, of 24 subjects who switched from either febuxostat group to allopurinol due to SUA ≥ 6.0 mg/dl, only 4 achieved SUA < 6.0 mg/dl with allopurinol 300 mg. It seems likely that more robust urate reduction could have been achieved by titration of the dose of allopurinol, as has been recommended in the recently published European League Against Rheumatism guidelines for gout management[3]. Nevertheless, neither the benefits nor the potential risks of titrating allopurinol dose beyond 300 mg daily have been evaluated in randomized clinical trials. Moreover, in current practice in the US, allopurinol is rarely prescribed at a dose exceeding 300 mg[21].

After adjusting rates of reported AE for duration of exposure to study drug, similar rates of AE and SAE were observed across treatments. Further, exposure-adjusted rates of AE resulting in premature discontinuation were comparable among groups. In addition, exposure-adjusted cardiac SAE rates reported in our study were comparable across treatment groups. On the other hand, all 10 deaths reported (6 attributed to cardiovascular causes) occurred among subjects receiving febuxostat. Despite differences in drug exposure, the absence of a clear mechanistic basis for adverse febuxostat-related cardiovascular events, and an absence of febuxostat dose- or time-relatedness to study deaths, cardiovascular safety with febuxostat in the gout population suggests the need for further evaluation. However, the overlapping confidence intervals for all 3 treatments illustrate the limits of these data in determining the significance of the differences in death rates. A higher death rate could be expected in this study population, as elevated SUA levels have been shown to significantly increase the risk of death from all causes, particularly among individuals at risk for cardiovascular disease[22].

Two responses to our findings seem worth considering: careful titration of allopurinol dose beyond the commonly given dose of 300 mg daily, as needed to achieve goal SUA range; or treatment with febuxostat. Although recommended in recently published guidelines for gout management[3], allopurinol dose titration beyond 300 mg daily requires validation with regard to safety and efficacy. Recently published evidence regarding allopurinol use in practice[21,23], however, suggests that even if the safety and efficacy of allopurinol at doses higher than 300 mg daily are established, a major educational effort will be required to encour-

age dose titration. In this context, febuxostat, which is now commercially available in the United States, may offer an attractive and clinically tested alternative to allopurinol in the urate-lowering management of patients with gout.

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