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Efficacy and Safety of Febuxostat Extended and Immediate Release in Patients With Gout and Renal Impairment: A Phase III Placebo-Controlled Study

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Objective. To assess the efficacy and safety of febuxostat extended release (XR) and immediate release (IR) in patients with gout and normal or impaired renal function.

Methods. This was a 3-month, phase III, multicenter, double-blind, placebo-controlled study. Patients (n = 1,790) with a history of gout and normal or impaired (mild-to-severe) renal function were randomized to receive placebo, febuxostat IR 40 or 80 mg, or febuxostat XR 40 or 80 mg once daily (1:1:1:1:1 ratio). End points included proportions of patients with a serum urate (UA) level of <5.0 mg/dl at month 3 (primary end point), a serum UA level of <6.0 mg/dl at month 3, and ≥1 gout flare requiring treatment over 3 months (secondary end points).

Results. Both febuxostat formulations led to significantly greater proportions of patients achieving a serum UA level of <5.0 mg/dl or <6.0 mg/dl at month 3 ($P < 0.001$ for all comparisons versus placebo). Equivalent doses of febuxostat XR and IR had similar treatment effects on serum UA level end points; however, a significantly greater proportion of patients achieved a serum UA level of <5.0 mg/dl with XR 40 mg versus IR 40 mg. Similar proportions of patients experienced ≥1 gout flare across treatment groups. Rates of treatment-emergent adverse events were low and evenly distributed between treatment arms. A preplanned subgroup analysis demonstrated that febuxostat formulations were well tolerated and generally effective on serum UA level end points (versus placebo) across all renal function subgroups.

Conclusion. Both formulations of febuxostat (XR and IR) were well tolerated and effective in patients with gout and normal or impaired renal function, including patients with severe renal impairment.

INTRODUCTION

Gout (urate crystal–induced arthritis) is a chronic disease associated with hyperuricemia, affecting approximately 8.3 million people in the US (1). Hyperuricemia is strongly linked to renal disease (2–7), and impaired renal function is an important risk factor for gout (8). It is estimated that approximately one-quarter of patients with gout have chronic stage ≥3 kidney disease (defined as an estimated glomerular filtration rate [eGFR] of <60 ml/minute/1.73 m^2) (9). There is a clinical need for a well-tolerated and effective treatment for hyperuricemia management in patients with gout and renal impairment.

Xanthine oxidase inhibitors, such as febuxostat immediate release (IR) and allopurinol, have been approved for the treatment of hyperuricemia (defined as serum urate [UA] levels above the limit of solubility [~6.8 mg/dl]) in patients with gout (10–13). Whereas febuxostat and allopurinol both lower urate levels by inhibiting xanthine oxidase, there are key differences in how they are metabolized and eliminated from the body in patients with renal impairment (10,13,14). Allopurinol and its principal active

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metabolite (oxypurinol) are primarily removed through renal pathways, and concerns relating to high doses and increased risk of adverse events (AEs) have been reported (10,14,15).

However, a recent study evaluating allopurinol dose escalation using a treat-to-target approach demonstrated that higher doses of allopurinol significantly lowered serum UA levels and were well tolerated; dose escalation with allopurinol was not associated with any differences in renal function change compared with maintenance of allopurinol dose (16). Consequently, an initial dosage of <100 mg/day, followed by slow titration in line with renal function (to ≥300 mg/day), is suggested in patients with gout and moderate-to-severe kidney disease (11). Conversely, febuxostat is primarily eliminated via the liver through hepatobiliary conjugation, which is not affected by renal impairment (13,17).

The efficacy and tolerability of febuxostat IR 40 mg and 80 mg once daily are well established in patients with gout who have normal renal function or mild-to-moderate renal impairment (17–22). Additionally, results from a recent phase II study suggested that febuxostat IR (30 mg twice daily and 40/80 mg once daily [dosage based on serum UA level on study day 14: patients with serum UA <6.0 mg/dl continued on 40 mg once daily and those with serum UA ≥6.0 mg/dl received 80 mg once daily from month 1]) was well tolerated and associated with significant urate lowering, without any significant deterioration in renal function, versus placebo in patients with gout and moderate-to-severe renal impairment (12). However, further evidence of the efficacy and safety of febuxostat in patients with renal impairment is needed, especially for patients with severe renal impairment.

To reduce the potential risk of treatment-initiated gout flares caused by fluctuations in drug exposure levels with febuxostat IR, an extended release (XR) formulation of febuxostat was developed with the aim of providing comparable or greater urate lowering with more stable drug exposure. Results from a phase I trial demonstrated that the XR formulation was associated with reduced exposure to febuxostat compared with the IR formulation (23). It has been hypothesized that the more stable drug exposure and reduced variability in daily serum UA levels associated with febuxostat XR may reduce the incidence of urate crystal–mediated inflammation and development of gout flares. In a phase II trial, febuxostat IR 30 mg twice daily (used to mirror the effect of XR 80 mg once daily) was more effective at lowering serum UA compared with placebo in patients with moderate-to-severe renal impairment (12). A subsequent phase II proof-of-concept study demonstrated that both IR and XR formulations had comparable efficacy on serum UA levels; the only significant treatment difference was a greater proportion of patients achieving a serum UA level of <5.0 mg/dl with febuxostat XR 40 mg versus the IR 40 mg formulation (24).

In this study, we present results from a 3-month, phase III, placebo-controlled study to investigate the efficacy and safety of febuxostat IR and XR in patients with gout and normal or impaired renal function, including a preplanned subgroup analysis of treatment effects in patients stratified by baseline renal function (from normal to severely impaired).

PATIENTS AND METHODS

Patients. In this phase III study comparing the efficacy and safety of febuxostat IR and XR, methodologies overlapped considerably with the above- mentioned phase II study in patients with gout and moderate renal impairment (24). The key differences between the 2 studies were a larger number of patients and a much broader gout patient population in the current study, including patients with normal renal function or mild-to-severe renal impairment. Eligible patients were age ≥18 years, had a history or presence of gout (defined as fulfilling the American Rheumatism Association (now the American College of Rheumatology) gout classification criteria) (25), a serum UA level of ≥8.0 mg/dl on the day –4 screening visit, and ≥1 gout flare within 12 months prior to screening. Patients were required to have an eGFR of ≥15 ml/minute at screening, and the protocol specified that ≥30% of enrolled patients should have moderate-to-severe renal impairment (eGFR of ≥15–59 ml/minute), with ≥85 of these patients having severe renal impairment (eGFR ≥15–29 ml/minute). Exclusion criteria included secondary hyperuricemia, history of xanthuria, and known hypersensitivity to febuxostat (for more exclusion criteria details, see Supplementary Appendix A, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40685/abstract).

Study design. This phase III, multicenter, randomized, double-blind, placebo-controlled study was conducted at 217 sites across the US from April 18, 2015 to November 18, 2016. The study was conducted in compliance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation guidelines for Good Clinical Practice, along with all applicable local regulations. The study protocol and related documents received institutional review board or ethics committee approval. All participants provided written informed consent prior to entering the study. The study design was previously described in the report on the related phase II study (24); briefly, the study consisted of a 3-week screening/washout period, followed by a 3-month double-blind treatment period (Figure 1).

Eligible patients received placebo or febuxostat IR 40 mg, XR 40 mg, IR 80 mg, or XR 80 mg orally once daily (randomized in a 1:1:1:1:1 ratio) for 3 months. Patients were randomized within 2 population strata based on baseline renal function: patients with severe renal impairment (eGFR ≥15–29 ml/minute) and without severe renal impairment (eGFR ≥30 ml/minute). An interactive voice or web-response technology was used for randomization and assigning the study drug. The study drug was self-administered as previously described (24).

All patients systematically received gout flare prophylaxis for the duration of double-blind treatment from day 1 to the end of treatment; colchicine 0.6 mg was administered every other

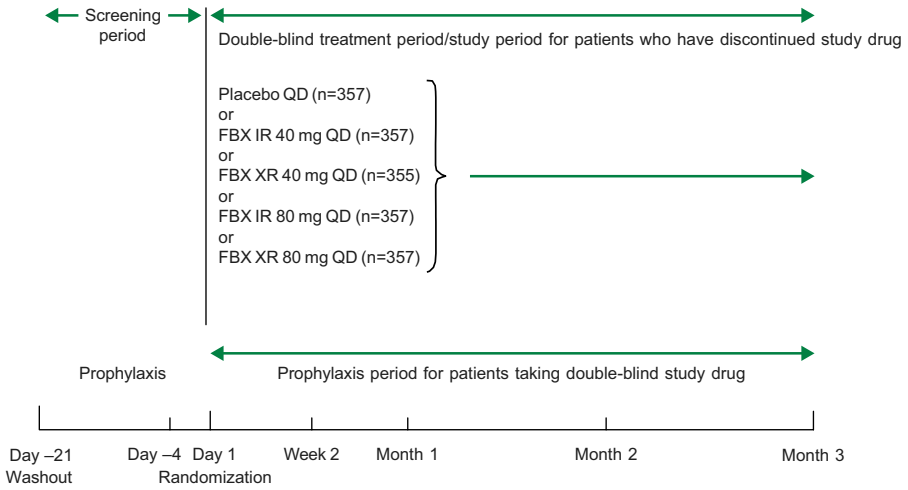

Figure 1. Study design. Subgroup numbers are from the full analysis set. In the safety analysis set, 1 patient was randomized to receive placebo but received febuxostat (FBX) immediate release (IR) 40 mg and so was included in the FBX IR 40 mg group. All patients received prophylaxis for gout flares over the 3-month double-blind treatment period. QD = once daily; XR = extended release.

day to patients with an eGFR of 15–59 ml/minute or once daily in patients with an eGFR of ≥60 ml/minute. However, if colchicine was not tolerated, naproxen 250 mg twice daily with lansoprazole 15 mg once daily was permitted in patients with an eGFR of ≥50 ml/minute; other nonsteroidal antiinflammatory drugs or prednisone were permitted at the discretion of the investigator. Beginning on the day –21 screening visit, patients discontinuing urate-lowering therapy received 0.6 mg colchicine every other day for gout flare prophylaxis until eGFR results were available.

Clinic visits occurred on days 1 and 14, and months 1 and 2; the final visit was on month 3 or with early termination. Clinical assessments (including vital signs, concomitant medication usage, and laboratory safety tests) were conducted during each of these visits, and samples were collected for clinical laboratory tests (including serum UA assessments) at all visits, except day 1.

Study end points. Primary and secondary end points were the same as those assessed in the related phase II study, i.e., the proportion of patients with a serum UA level of <5.0 mg/dl at month 3 was the primary end point, and the proportion of patients with a serum UA level of <6.0 mg/dl at month 3 and the proportion of patients with ≥1 gout flare requiring treatment during the 3-month treatment period were the secondary efficacy end points (24).

Based on the pharmacokinetic and pharmacodynamic characteristics of the XR formulation (23), greater serum UA level reductions were expected with febuxostat XR than with febuxostat IR; therefore, the more difficult-to-achieve target of a serum UA level of <5.0 mg/dl was selected for the primary end point to compare the efficacy of the XR and IR formulations. The recommended target level to ensure better disease control for patients receiving urate-lowering therapy with severe disease and high urate burden is a serum UA level of <5.0 mg/dl, and a serum UA level of <6.0 mg/dl is the recommended target level for most patients with gout (11,26).

Safety and tolerability assessments included incidence of treatment-emergent AEs (TEAEs), findings from 12-lead electrocardiograms, clinical laboratory assessments, and vital signs. As in the related phase II study (24), a TEAE was defined as any AE, regardless of its relationship to the study drug, occurring from day 1 through 30 days after the last dose of the double-blind study drug. TEAEs were identified as reported by the investigators and summarized using the terminology of the Medical Dictionary for Regulatory Activities (version 18.0). AEs were summarized as any TEAE, treatment-related TEAEs, TEAEs leading to discontinuation of the study drug, serious TEAEs, and death.

Statistical analysis. Efficacy outcomes were assessed using the full analysis set, which included all patients who were randomized for treatment and received ≥1 dose of study drug. Notable changes to the original trial protocol are summarized in Supplementary Appendix B, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40685/abstract. Efficacy outcomes were compared between treatment groups using the Cui, Hung, and Wang Z test statistic (see Supplementary Appendix C, available at http://onlinelibrary.wiley.com/doi/10.1002/art.40685/abstract). A closed testing strategy was prespecified for the primary and secondary end points to adjust for comparisons between the 2 doses (40 and 80 mg); only *P* values less than 0.025 were considered statistically significant. A gout flare was defined as previously described (24). Safety outcomes were evaluated using the safety analysis set (all patients who received ≥1 dose of study drug), and patients were analyzed according to the treatment they received.

A sample size of 1,750 patients (350 per treatment group) was targeted to provide ≥90% power to detect a 14% difference

between febuxostat XR and the corresponding febuxostat IR dose or placebo, using a 2-sided Fisher's exact test at a significance level of 2.5%.

For preplanned subgroup analysis, treatment effects on the proportion of patients achieving serum UA level targets and safety end points were also assessed in patient populations stratified by level of renal function at baseline. The classification of renal impairment was as follows: normal renal function, eGFR ≥90 ml/minute; mild renal impairment, eGFR ≥60–89 ml/minute; moderate renal impairment, eGFR ≥30–59 ml/minute; and severe renal impairment, eGFR ≥15–29 ml/minute.

RESULTS

Findings in the patient population. Of 3,654 patients screened, 1,097 (30.0%) and 767 (21.0%) were not enrolled due to screening failure and washout failure, respectively; the primary reason was failure to meet the entry criteria (870 of 1,097 patients [79.3%] and 487 of 767 patients [63.5%], respectively). Overall, 1,790 patients (49.0%) were enrolled and randomized to treatment (see Supplementary Figure 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40685/abstract). A total of 1,783 randomized patients (99.6%) received ≥1 dose of study drug (full and safety analysis sets). The percentages of early discontinuations were similar across treatment groups (14.5–19.0%).

Patient characteristics at baseline were similar across treatment arms (Table 1). The patient cohort was predominantly male (88.4%) and white (64.3%), with a mean age of 55.1 years (range 24–94 years) and mean ± SD body mass index of 34.3 ± 7.8 kg/m^2. The overall mean ± SD serum UA level at baseline was 9.61 ± 1.27 mg/dl, and ~65.1% of patients had a baseline serum UA level of ≥9.0 mg/dl. Approximately 88% of patients had a gout flare within 6 months prior to study enrollment; the majority of patients (59.2%) had received prior treatment with urate-lowering therapy. The proportion of patients in each base-

Table 1. Demographic information and characteristics of the patients at baseline*

	Placebo (n = 357)	FBX IR 40 mg (n = 357)	FBX XR 40 mg (n = 355)	FBX IR 80 mg (n = 357)	FBX XR 80 mg (n = 357)
Age, mean ± SD years	54.4 ± 11.6	55.5 ± 11.1	55.1 ± 12.7	54.9 ± 11.3	55.4 ± 11.9
Sex, no. (%)					
Men	316 (88.5)	311 (87.1)	312 (87.9)	315 (88.2)	323 (90.5)
Women	41 (11.5)	46 (12.9)	43 (12.1)	42 (11.8)	34 (9.5)
Race, no. (%)†					
White	231 (64.7)	235 (65.8)	226 (63.7)	230 (64.4)	225 (63.0)
Black/African American	94 (26.3)	89 (24.9)	100 (28.2)	98 (27.5)	93 (26.1)
BMI, mean ± SD kg/m^2	34.9 ± 8.3‡	34.3 ± 8.0	34.3 ± 8.1	33.7 ± 7.5	34.1 ± 7.2
Baseline serum UA, mean ± SD mg/dl§	9.7 ± 1.4	9.6 ± 1.2	9.5 ± 1.2	9.6 ± 1.3	9.7 ± 1.3
Approximate gout flares during past year, no. (%)§					
1–3	196 (55.1)	200 (55.9)	213 (60.0)	203 (56.9)‡	214 (59.9)
4–6	102 (28.7)	97 (27.1)	92 (25.9)	93 (26.1)	85 (23.8)
>6	58 (16.3)	61 (17.0)	50 (14.1)	60 (16.8)	58 (16.2)
Renal function at baseline, no. (%)					
Severely impaired	18 (5.0)	23 (6.4)	21 (5.9)	20 (5.6)	18 (5.0)
Moderately impaired	93 (26.1)	91 (25.5)	93 (26.2)	106 (29.7)	100 (28.0)
Mildly impaired	194 (54.3)	192 (53.8)	196 (55.2)	185 (51.8)	198 (55.5)
Normal	52 (14.6)	51 (14.3)	45 (12.7)	46 (12.9)	41 (11.5)

* Except where indicated otherwise, data are from the full analysis set. BMI = body mass index; UA = urate.
† The total number (%) of patients classified as American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, and Other were 7 (0.4), 112 (6.3), 20 (1.1), and 23 (1.3), respectively.
‡ Data are missing for 1 patient for this variable in this treatment group.
§ Data are from the safety analysis set: placebo (n = 356), febuxostat (FBX) immediate release (IR) 40 mg (n = 358), FBX extended release (XR) 40 mg (n = 355), FBX IR 80 mg (n = 357), and FBX XR 80 mg (n = 357).

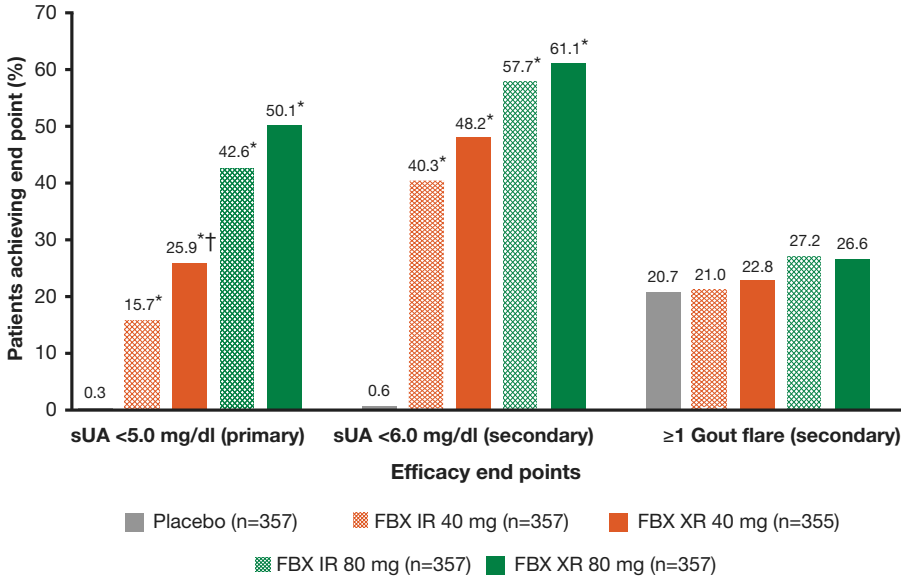

Figure 2. Percentage of patients (in full analysis set) who achieved primary and secondary outcomes. Based on multiplicity adjustment, the level of significance was set at $P < 0.025$ for primary comparisons. * = $P < 0.001$ versus placebo. † = $P = 0.001$ versus equivalent-dose immediate release (IR) formulation. FBX = febuxostat; XR = extended release.

line renal function subgroup category was comparable across treatment groups (Table 1).

Efficacy. *Primary efficacy end point*. Significantly greater proportions of patients treated with febuxostat (both formulations and doses) had achieved a serum UA level of <5.0 mg/dl at month 3 compared with patients who received placebo ($P < 0.001$ for all comparisons) (see Figure 2 and Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40685/abstract). Febuxostat XR 40 mg was associated with a significantly greater proportion of patients achieving a serum UA level of <5.0 mg/dl at month 3 versus IR 40 mg (25.9% versus 15.7%; $P = 0.001$). Although a numerically greater proportion of patients treated with febuxostat XR 80 mg achieved a serum UA level of <5.0 mg/dl at month 3 compared with patients treated with IR 80 mg, the difference was not statistically significant.

Secondary efficacy end points. Both formulations and doses of febuxostat treatment were associated with significantly greater proportions of patients achieving a serum UA level of <6.0 mg/dl at month 3 versus placebo ($P < 0.001$ versus placebo for all comparisons). However, there were no significant differences in the treatment effect of equivalent doses of XR and IR for this end point. The proportions of patients with ≥1 gout flare requiring treatment during the 3-month treatment period were similar across treatment groups (Figure 2 and Supplementary Table 1, available at http://onlinelibrary.wiley.com/doi/10.1002/art.40685/abstract).

Analysis of serum UA end points in renal function subgroups. Febuxostat IR and XR (both doses) were associated with significantly greater proportions of patients achieving the primary end point of a serum UA level of <5.0 mg/dl at month 3 versus placebo across all renal function subgroups with the exception of febuxostat XR 40 mg in patients with severe renal impairment ($P < 0.05$ for all other comparisons) (see Figure 3A and Supplementary Table 2, available at http://onlinelibrary.wiley.com/doi/10.1002/art.40685/abstract). Similarly, both formulations and doses of febuxostat were associated with consistent treatment benefits in the proportions of patients achieving a serum UA level of <6.0 mg/dl at month 3 across all renal function subgroups versus placebo ($P \leq 0.001$ for all comparisons versus placebo) (see Figure 3B and Supplementary Table 2, available at http://onlinelibrary.wiley.com/doi/10.1002/art.40685/abstract).

Compared with febuxostat IR 40 mg, febuxostat XR 40 mg was associated with a significantly greater proportion of patients achieving a serum UA level of <5.0 mg/dl in patients with moderate renal impairment (26.9% versus 13.2%; $P = 0.02$) or mild renal impairment (29.1% versus 16.1%; $P = 0.001$), as well as with a greater proportion of patients achieving a serum UA level of <6.0 mg/dl in patients with mild renal impairment (49.5% versus 38.0%; $P = 0.016$) (see Figures 3A and B and Supplementary Table 2, available at http://onlinelibrary.wiley.com/doi/10.1002/art.40685/abstract). However, there were no other significant differences in the treatment effect of equivalent doses of XR and IR on these end points in any other renal function subgroups. The proportions of patients with ≥1 gout flare requiring treatment during the 3-month treatment period were generally comparable

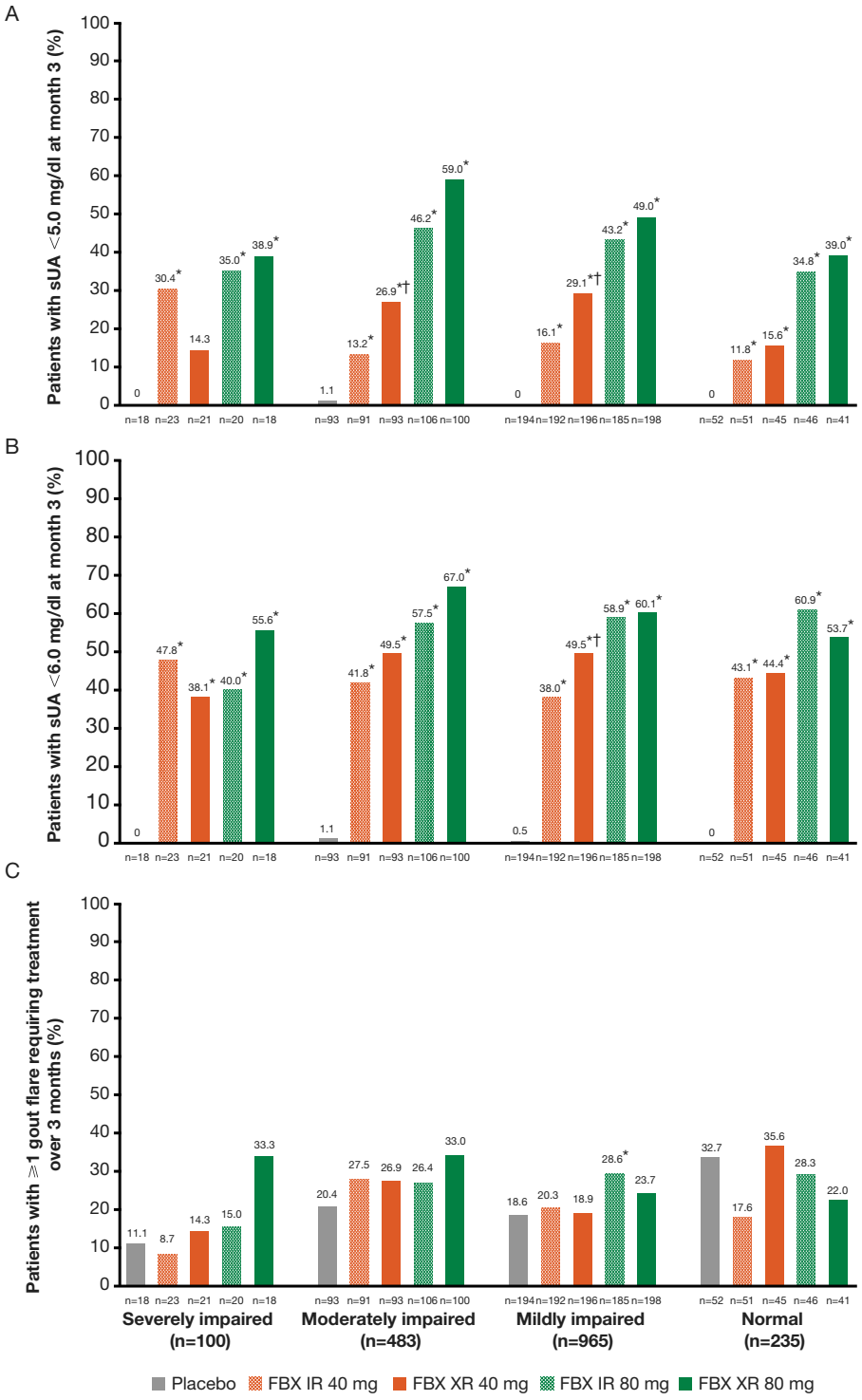

Figure 3. Renal subgroup analysis, with treatment group comparisons were based on the Cui, Hung, and Wang Z test statistic. **A,** Percentage of patients who achieved a serum urate (sUA) level of <5.0 mg/dl (primary end point) at month 3. * = $P < 0.05$ versus placebo; † = $P < 0.05$ versus equivalent-dose immediate release (IR) formulation. **B,** Percentage of patients who achieved a serum UA level of <6.0 mg/dl at month 3. * = $P \leq 0.001$ versus placebo; † = $P < 0.05$ versus equivalent-dose IR formulation. **C,** Percentage of patients who experienced ≥1 gout flare that required treatment over the 3-month study period. * = $P < 0.05$ versus placebo. Patients were stratified by baseline renal function; normal renal function was defined as an estimated glomerular filtration rate (eGFR) of ≥90 ml/minute, mild renal impairment as an eGFR of ≥60–89 ml/minute, moderate renal impairment as an eGFR of ≥30–59 ml/minute, and severe renal impairment as an eGFR of ≥15–29 ml/minute. FBX = febuxostat; XR = extended release.

Table 2. Overview of patients experiencing TEAEs, treatment-related TEAEs, and serious TEAEs*

	Placebo (n = 356)	FBX IR 40 mg (n = 358)	FBX XR 40 mg (n = 355)	FBX IR 80 mg (n = 357)	FBX XR 80 mg (n = 357)
Overall TEAEs	134 (37.6)	147 (41.1)	119 (33.5)	143 (40.1)	148 (41.5)
Related to treatment	25 (7.0)	29 (8.1)	21 (5.9)	22 (6.2)	32 (9.0)
Not related to treatment	109 (30.6)	118 (33.0)	98 (27.6)	121 (33.9)	116 (32.5)
TEAEs by severity					
Mild	59 (16.6)	70 (19.6)	53 (14.9)	69 (19.3)	84 (23.5)
Moderate	64 (18.0)	61 (17.0)	57 (16.1)	59 (16.5)	57 (16.0)
Severe	11 (3.1)	16 (4.5)	9 (2.5)	15 (4.2)	7 (2.0)
TEAEs leading to study drug discontinuation	9 (2.5)	9 (2.5)	10 (2.8)	13 (3.6)	6 (1.7)
Serious TEAEs	8 (2.2)	12 (3.4)	6 (1.7)	8 (2.2)	8 (2.2)
Related to treatment	0	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Not related to treatment	8 (2.2)	11 (3.1)	5 (1.4)	7 (2.0)	7 (2.0)
Leading to study drug discontinuation	2 (0.6)	3 (0.8)	3 (0.8)	4 (1.1)	1 (0.3)
Deaths	1 (0.3)	0	1 (0.3)	1 (0.3)	0

* Values are the number (%) of patients in the safety analysis set experiencing any treatment-emergent adverse events (TEAEs). One patient was randomized to receive placebo but received febuxostat (FBX) immediate release (IR) 40 mg and so was included in the FBX IR 40 mg group. XR = extended release.

across treatment groups within each of the renal function subgroups (see Figure 3C and Supplementary Table 2, available at http://onlinelibrary.wiley.com/doi/10.1002/art.40685/abstract).

Safety and tolerability. TEAEs, treatment-related TEAEs, and serious TEAEs across treatment groups are summarized in Table 2. Overall, 38.8% of patients (691 of 1,783) experienced at least 1 TEAE. In most of these patients (633 of 691 [91.6%]), TEAEs were mild or moderate in intensity, and no apparent patterns were observed in relation to the dose level or formulation of febuxostat. The incidences of treatment-related TEAEs (129 of 1,783 [7.2%]) and serious TEAEs (42 of 1,783 [2.4%]) were low across all treatment groups.

The most common TEAEs (reported by ≥2% of patients in any treatment group) are described in Table 3, with diarrhea, nasopharyngitis, and hypertension most commonly experienced by patients. The overall incidence of treatment-related TEAEs was relatively low; among these, there were 2 cases of renal failure (reported as renal insufficiency or worsening renal insufficiency, with 1 patient each in the febuxostat XR 40 mg and IR 40 mg treatment groups), 1 case of acute kidney injury (reported as acute renal insufficiency [with febuxostat XR 40 mg]), and 1 case of renal impairment (reported as worsening kidney function [with febuxostat IR 40 mg]). The incidence of increased blood levels of creatinine appeared to be slightly higher with febuxostat IR 80 mg group (2%) compared with the other febuxostat treatment groups (0.8%).

The overall incidence of serious TEAEs was low and generally similar across treatment groups. Serious TEAEs included 3 fatal AEs, 2 of which were considered unrelated to the study drug (1 fatal cardiac arrest in a patient with severe renal impairment in the placebo group and 1 fatal worsening of hypertensive cardiovascular disease in a patient with mild renal impairment in the febuxostat XR 40 mg group) and another that was considered to be related to the study drug (fatal cardiorespiratory arrest in a patient with severe renal impairment in the febuxostat IR 80 mg group). Three other patients had nonfatal serious TEAEs that were considered to be related to the study drug: with febuxostat IR 40 mg (severe renal impairment subgroup), 1 patient had serious TEAEs of renal impairment and abdominal pain: with febuxostat XR 40 mg (severe renal impairment subgroup), with 1 patient had acute respiratory failure and angioedema; and with febuxostat XR 80 mg (mild renal impairment subgroup), 1 patient had peripheral edema.

The medical histories of patients with fatal serious TEAEs and serious TEAEs related to treatment are summarized in Supplementary Table 3 (available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40685/abstract). The overall incidence of TEAEs leading to discontinuation of the study drug (47 of 1,783 [2.6%]) was low and similar across treatment groups (Table 2). The majority of TEAEs leading to discontinuation of the study drug were single occurrences and were generally distributed across treatment groups with no apparent trends.

Analysis of safety and tolerability in renal function subgroups. The overall incidence of TEAEs was similar across treatment groups within each of the renal function subgroups, as was the incidence of treatment-related TEAEs (see Supplementary Table 4, available at http://onlinelibrary.wiley.com/doi/10.1002/art.40685/abstract). There were no apparent trends observed between febuxostat dose or formulation and incidence of TEAEs. The incidences of the 5 most commonly reported TEAEs (diarrhea, hypertension, nasopharyngitis, arthralgia, and upper respiratory tract infection) were evenly distributed across the renal function sub-

Table 3. Most common TEAEs recorded in ≥2% of patients in any treatment group*

	Placebo (n = 356)	FBX IR 40 mg (n = 358)	FBX XR 40 mg (n = 355)	FBX IR 80 mg (n = 357)	FBX XR 80 mg (n = 357)
Gastrointestinal disorders					
Diarrhea	13 (3.7)	9 (2.5)	9 (2.5)	21 (5.9)	9 (2.5)
Infections and infestations					
Nasopharyngitis	11 (3.1)	7 (2.0)	7 (2.0)	9 (2.5)	4 (1.1)
Upper respiratory tract infection	4 (1.1)	6 (1.7)	6 (1.7)	5 (1.4)	8 (2.2)
Laboratory abnormalities					
Alanine aminotransferase increased	6 (1.7)	7 (2.0)	8 (2.3)	2 (0.6)	4 (1.1)
Aspartate aminotransferase increased	3 (0.8)	3 (0.8)	7 (2.0)	3 (0.8)	2 (0.6)
Blood creatinine increased	1 (0.3)	3 (0.8)	3 (0.8)	7 (2.0)	3 (0.8)
Gamma glutamyl transferase increased	3 (0.8)	6 (1.7)	6 (1.7)	7 (2.0)	5 (1.4)
Musculoskeletal and connective tissue disorders					
Arthralgia	7 (2.0)	8 (2.2)	5 (1.4)	6 (1.7)	4 (1.1)
Nervous system disorders					
Headache	6 (1.7)	6 (1.7)	8 (2.3)	4 (1.1)	4 (1.1)
Respiratory, thoracic, and mediastinal disorders					
Cough	5 (1.4)	9 (2.5)	2 (0.6)	3 (0.8)	1 (0.3)
Vascular disorders					
Hypertension	10 (2.8)	13 (3.6)	6 (1.7)	8 (2.2)	5 (1.4)

* Values are the number (%) of patients in the safety analysis set reporting any treatment-emergent adverse events (TEAEs; by system organ class/preferred term). One patient was randomized to receive placebo but received febuxostat (FBX) immediate release (IR) 40 mg and so was included in the FBX IR 40 mg group. XR = extended release.

groups (see Supplementary Table 5, available at http://onlinelibrary.wiley.com/doi/10.1002/art.40685/abstract). Not surprisingly, the overall incidence of TEAEs was higher in the severe renal impairment subgroup than in the other renal function subgroups.

DISCUSSION

The febuxostat XR formulations were developed with the aim of providing comparable or superior urate-lowering efficacy versus their febuxostat IR counterparts, with reductions in treatment-initiated flares due to a more stable drug exposure profile. The current phase III study assessed the tolerability and efficacy of febuxostat IR 40 and 80 mg once daily (currently approved dosages) compared with XR formulations at the same dosages. The inclusion of a placebo arm permitted comparisons of the safety and efficacy of all febuxostat treatment regimens versus placebo. In addition, preplanned subgroup analyses were conducted to evaluate treatment effects in patients stratified by baseline renal function.

Several key findings were demonstrated in this phase III study. First, both the XR and IR formulations of febuxostat were generally well tolerated and were associated with significant reductions in serum UA levels compared with placebo in patients with gout and normal or impaired renal function. The incidences of renal TEAEs were relatively low and evenly distributed across treatment groups, with 1 case of fatal cardiorespiratory arrest in a patient with severe renal impairment (febuxostat IR 80 mg group) and 1 serious renal TEAE (a case of renal impairment in the febuxostat IR 40 mg group) considered to be related to febuxostat treatment. Second, the statistically significant treatment benefits in favor of febuxostat (versus placebo) were also generally seen across all renal function subgroups, including patients with severe renal impairment. Third, analysis of the safety data demonstrated that there were no large differences in TEAEs across treatment arms in patients with gout stratified by baseline renal function. These findings provide further evidence of the tolerability and efficacy of febuxostat in patients with gout and normal or impaired renal function, including patients with severe renal impairment.

The results of this study also indicated that equivalent doses of febuxostat XR and IR had similar treatment effects on serum UA levels; in the overall population, the only statistically significant treatment difference between formulations was the greater proportion of patients achieving a serum UA level of <5.0 mg/dl at month 3 seen with febuxostat XR 40 mg versus IR 40 mg. It is worth noting that febuxostat IR 80 mg was consistently more effective at controlling serum UA levels than febuxostat XR 40 mg, suggesting that dose titration from febuxostat IR 40 mg to febuxostat IR 80 mg would potentially represent a more effective treatment strategy than switching to febuxostat XR 40 mg. Febuxostat XR 80 mg was not associated with any statistically significant treatment benefits

on serum UA level <5.0 mg/dl or serum UA level <6.0 mg/dl treatment target end points compared with febuxostat IR 80 mg. In addition, the proportions of patients with ≥1 gout flare requiring treatment during the 3-month treatment period were similar across active treatment groups, suggesting that the XR formulation did not reduce the incidence of treatment-initiated gout flares compared with the IR formulation.

These results were similar to those from a 3-month phase II study in patients with moderate renal function, which demonstrated that treatment with febuxostat XR or IR led to significant urate lowering versus placebo, as well as indicated that equivalent doses of febuxostat XR and IR had similar treatment effects on serum UA levels (24). The only significant treatment difference between equivalent doses of febuxostat XR and IR was the greater proportion of patients achieving a serum UA level of <5.0 mg/dl at month 3 with febuxostat XR 40 mg versus IR 40 mg. Although febuxostat XR 40 mg was associated with a numerically lower proportion of patients with ≥1 gout flare requiring treatment compared with febuxostat IR 40 mg during the phase II study, the difference was not statistically significant. The absence of any significant treatment benefit in favor of febuxostat XR on the incidence of treatment-initiated gout flares is consistent with findings from the current phase III study.

The current results do, however, add to the growing evidence supporting the use of febuxostat in the management of hyperuricemia in patients with renal impairment. Data from clinical trials have demonstrated that febuxostat IR is effective and well tolerated in patients with mild-to-moderate renal impairment (19,20,27,28). Two long-term open-label studies demonstrated that febuxostat IR not only lowered serum UA levels, but was also associated with more stable and even improved renal function (27,28). In a 5-year open-label study, febuxostat (IR 40, 80, or 120 mg) was well tolerated and effective at reducing serum UA levels in patients with normal and impaired renal function (22). Subanalyses of data from a separate 4-year open-label trial demonstrated that febuxostat (IR 80 or 120 mg) consistently reduced serum UA levels from baseline by ~50% (28). In post hoc analyses of these long-term trials, it was estimated that each 1 mg/dl of sustained reduction of serum UA levels brought about by urate-lowering treatment could potentially lead to preservation of 1.0–1.15 ml/minute of eGFR (27,28).

While substantial evidence supports the efficacy and safety of febuxostat IR in patients with gout and normal or mildly impaired renal function, data regarding the effects of febuxostat IR treatment are less robust in patients with gout and moderate renal impairment, and are very limited in patients with severe renal impairment (12). Findings from a recent phase II study suggested that both febuxostat IR 30 mg twice daily and febuxostat IR 40 or 80 mg (depending on a serum UA level of <6.0 or ≥6.0 mg/dl on study day 14) once daily significantly lowered serum UA levels compared with placebo in patients with gout and moderate-to-severe renal impairment (eGFR 15–50 ml/minute/1.73 m^2). Critically, these treatment benefits were not associated with any significant deterioration in renal function (12). These findings are supported by those from the current renal subgroup analysis, which showed that, in general, all formulations and doses of febuxostat were effective and well tolerated across all renal function subgroups, including patients with severe renal impairment.

Treatment options for patients with gout and renal impairment are limited. Despite allopurinol being relatively well tolerated and effective at reducing serum UA in patients with gout (10), its elimination via the kidneys complicates its use in patients with impaired renal function. Previous publications have suggested that a dose reduction of allopurinol in patients with gout and renal impairment may limit its effectiveness on serum UA treatment targets (20,29,30) and potentially lead to suboptimal treatment in clinical practice (31). However, a recent study evaluating dose escalation with allopurinol suggested that higher doses were effective in lowering serum UA levels to treatment target in most people with gout and were well tolerated (16).

Febuxostat IR 80 mg or IR 120 mg has been shown to be more efficacious than allopurinol 300 mg (the most commonly used fixed daily dose) in lowering serum UA levels to <6.0 mg/dl and maintaining this level in patients with gout and mild to moderately impaired renal function (18).

The current phase III study has several benefits and limitations. This trial represents the largest investigation of febuxostat in patients with renal impairment, including severe renal impairment, and the stratification of randomization by renal function (severe or not severe) helped to maintain a balanced distribution of patients with various degrees of renal impairment across treatment groups at baseline. While the sample size was adequate to demonstrate the efficacy of both formulations of febuxostat in the overall patient population and across renal function subgroups, the small sample sizes seen in the renal function subgroups are associated with greater variability, and any significant differences, or lack thereof, should therefore be interpreted with caution. It is also important to note that the use of gout flare prophylaxis in this study is likely to have limited the possibility of detecting any benefits of the XR formulation over the IR formulation in reducing the incidence of treatment-initiated gout flares.

In conclusion, the results from this phase III study demonstrated that febuxostat IR and XR formulations were both well tolerated and effective in patients with gout and normal renal function or mild-to-severe renal impairment. However, the incidence of treatment-initiated gout flares was not reduced with the XR formulation compared with the IR formulation. The present findings, together with those from recent phase II trials in patients with gout and moderate or moderate-to-severe renal impairment (12,24), support the view that febuxostat IR has the

potential to help address the treatment of gout in patients with renal impairment.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Saag 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 conception and design. Saag, Becker, Whelton, Hunt, Gunawardhana.

Acquisition of data. Saag, Castillo.

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ROLE OF THE STUDY SPONSOR

Takeda Pharmaceuticals International was involved in the design and conduct of the study, all study analyses, the drafting and the editing of the manuscript, and its final contents. All authors made the decision to submit the manuscript for publication. Medical writing assistance was provided by Stephen Craig (Caudex, New York) and funded by Takeda Pharmaceuticals International. Publication of this article was not contingent upon approval by Takeda Pharmaceuticals International.

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