Clinical Drug Investigation (2018) 38:1135–1143
https://doi.org/10.1007/s40261-018-0699-0

ORIGINAL RESEARCH ARTICLE

Multicenter, Open-Label Study of Long-Term Topiroxostat (FYX-051) Administration in Japanese Hyperuricemic Patients with or Without Gout

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Published online: 15 September 2018

Abstract

Background and Objectives Topiroxostat—a novel selective xanthine oxidoreductase inhibitor—has been reported to reduce serum urate levels. The purpose of this study was to assess the efficacy and safety of long-term topiroxostat administration in Japanese hyperuricemic patients with or without gout.

Methods This multicenter, open-label study evaluated the efficacy and safety of long-term twice-daily oral topiroxostat administration in patients with or without gout. The initial topiroxostat dosage was 40–80 mg/day, and the maintenance dosage was 120 mg/day, which was increased to 240 mg/day at 40 mg increments if the serum urate level exceeded 6.0 mg/dL.

Results Serum urate level, which was the primary endpoint, decreased stably over time and showed significant reduction on the final visit (38.44% ± 13.34%) compared with that at the baseline. Both urinary albumin/creatinine ratio and mean blood pressure significantly improved. The overall incidence rate of adverse drug reactions to topiroxostat was 67.8%; on the final visit, the rate of adverse drug reactions was 66.7% with 120 mg/day, 72.2% with 160 mg/day, 53.8% with ≥ 200 mg/day, and 100% with the other dosages. On the final visit, the incidence of gouty arthritis, for which a causal relationship with topiroxostat could not be ruled out, was 4.1% overall, 4.8% with 120 mg/day, 0% with 160 mg/day, and 7.7% with ≥ 200 mg/day.

Conclusions We verified the efficacy and safety of 58-week oral topiroxostat administration at stepwise increments to up to 240 mg/day.

Study Registration JAPIC CTI-101068.

Key Points

In this study, the efficacy and safety of 58-week administration of the novel non-purine selective xanthine oxidoreductase inhibitor, topiroxostat, were verified.

Topiroxostat not only lowered the serum urate but also decreased urinary albumin levels, corrected for urinary creatinine levels, suggesting a likely renoprotective action.

Topiroxostat seems to be a promising therapeutic drug for gout or hyperuricemia.

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1 Introduction

Hyperuricemia (defined as serum urate level ≥ 7.0 mg/dL in Japan) is a causative factor for urate deposition diseases such as urolithiasis and gouty arthritis [1]. A major target of treating hyperuricemia to prevent gouty arthritis is to reduce and maintain the serum urate levels at < 6.0 mg/dL [2–5]. On the other hand, recent studies have shown that hyperuricemia causes renal impairment and it is related to the development and progression of chronic kidney disease [6–8]. Interventional studies have shown that serum urate-lowering drugs, such as allopurinol, are effective in maintaining the renal function in patients with chronic kidney disease [9, 10].

Topiroxostat (FYX-051) is a novel, non-purine, selective xanthine oxidoreductase inhibitor [11], which belongs to the group of urate production inhibitors, and is used to treat gout/hyperuricemia in Japan. Topiroxostat is a hybrid-type inhibitor that inhibits enzyme activity by covalent bonding with molybdenum, which is the reaction center of xanthine oxidoreductase, and by interaction with amino acid residues in the substrate-binding pocket [12–14].

A phase II dose-setting and -verification study conducted in Japan has shown that topiroxostat decreases serum urate levels dose-dependently [15, 16]. Furthermore, the non-inferiority of topiroxostat to allopurinol in serum urate-lowering rate has been confirmed in a phase III study [17]. The serum urate-lowering action and tolerability of topiroxostat without dose adjustment have also been demonstrated in a double-blind placebo-controlled study conducted in hyperuricemic patients with or without gout who had concurrent moderate stage 3 renal impairment. The pharmacokinetics of unchanged topiroxostat or its metabolites is unaffected by mild-to-moderate renal impairment, and in patients with concurrent moderate renal impairment and hyperuricemia, it has been reported to lower the serum urate levels and urinary albumin levels [18]. In another study, in which the impact of topiroxostat on QT/QTc was evaluated, it has been shown that topiroxostat does not prolong QT/QTc at 60 mg/day and 180 mg/day [19].

Accumulating evidence has proved the efficacy and safety of topiroxostat over the years, but the efficacy and safety of long-term administration has not yet been fully investigated. Therefore, the results of 58-week treatment with oral topiroxostat in hyperuricemic patients with or without gout are reported in this study.

2 Patients and Methods

2.1 Study Design

In this multicenter, open-label study, hyperuricemic patients with or without gout were treated with oral topiroxostat twice daily at 40 mg/day for 2 weeks and 80 mg/day for 4 weeks in the initial period, followed by 120 mg/day for 52 weeks in the maintenance period. The dosage during the maintenance period was increased stepwise if the serum urate level was > 6.0 mg/dL and patient tolerability allowed it (it was increased up to 120 mg/day in all patients, and then at 40 mg/day increments up to 240 mg/day). The dosage of topiroxostat is expressed per day, unless otherwise specified in this study. The topiroxostat dosage in each administration period is shown in Fig. 1. The number of patients was designed according to ICH-E1 guidelines; 100 patients exposed for 1 year was considered to be acceptable to assure the safety data. In the run-in period of 1–4 weeks, we screened and enrolled eligible subjects.

2.2 Inclusion and Exclusion Criteria

Patients were included in this study if they met the following inclusion criteria: Japanese patients aged 20–75 years who were able to provide written informed consent, with serum urate levels in the run-in period of ≥ 7.0 mg/dL in patients with uric acid tophi or a history of gout attacks or ≥ 9.0 mg/dL in patients with hyperuricemia (however, ≥ 8.0 mg/dL in patients who were receiving administration for or had a diagnosis of urolithiasis, hypertension, hyperlipidemia, or diabetes).

Patients were excluded from the study if they met the following exclusion criteria: onset of gouty arthritis within 2 weeks prior to the start of study drug administration; specific disorders causing primary or secondary hyperuricemia, e.g. Lesch–Nyhan syndrome, hematologic malignancies, or Down's syndrome; HbA1c ≥ 8.0%; renal function impairment [estimate glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2]; liver impairment (alanine aminotransferase ≥ 100 U/L and/or aspartate transaminase ≥ 100 U/L), severe hypertension (systolic blood pressure ≥ 180 mmHg and/or diastolic blood pressure ≥ 110 mmHg); and the use of urate-lowering agents, azathioprine, 6-mercaptopurine, theophylline, other study drugs than topiroxostat, or agents considered to affect the outcome during the period from 2 weeks prior to the start of the pre-observation period until the day of administration commencement.

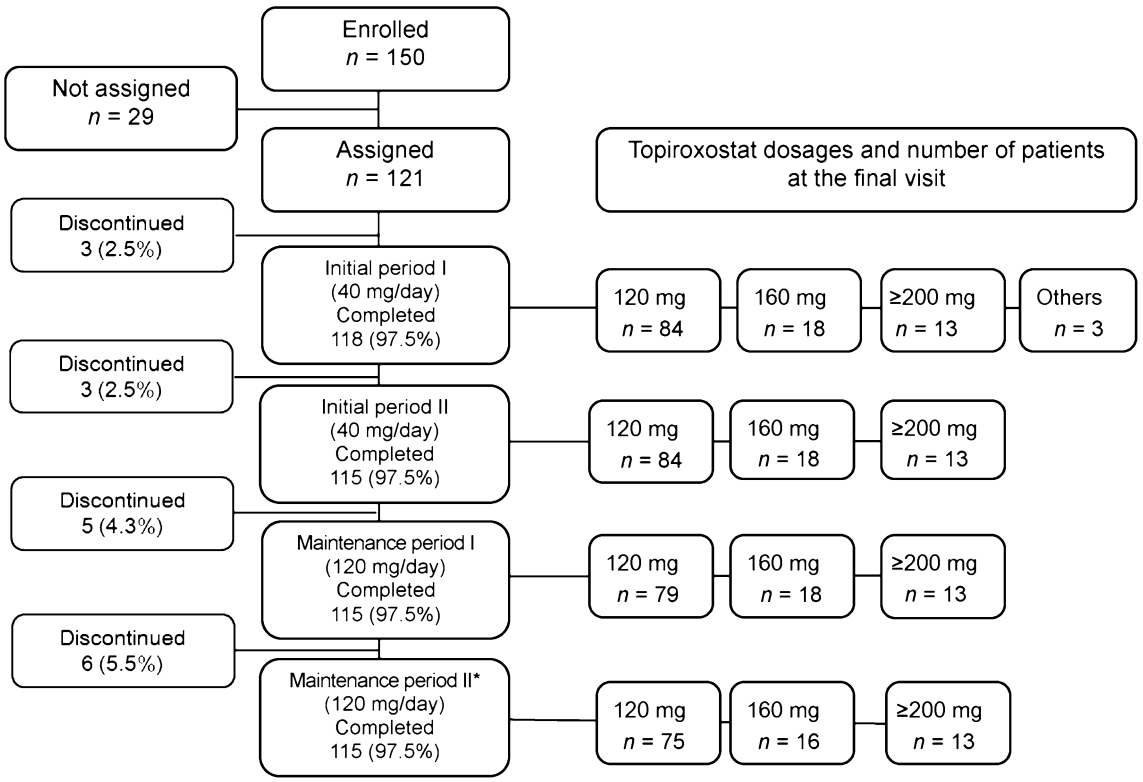

Fig. 1 Study design. *The maintenance dosage was increased to 160 mg/day after 18 weeks of treatment, if the serum urate level after 14 weeks of treatment was > 6.0 mg/dL. It was further increased from 160 to 200 mg/day after 30 weeks of treatment, if the serum urate level after 26 weeks of treatment (8 weeks after the first increase) was > 6.0 mg/dL. It was then increased from 200 to 240 mg/day after 42 weeks of treatment, if the serum urate level after 38 weeks of treatment (8 weeks after the second increase) was > 6.0 mg/dL. The maintenance dosage was not increased, even if the serum urate level was > 6.0 mg/dL at the time of dosage increase, if it had been ≤ 6.0 mg/dL after 14 or 26 weeks of treatment

2.3 Endpoints

The primary efficacy endpoint was the serum urate-lowering rate at the final visit, relative to the baseline level. The secondary endpoints were the achievement rate of patients who achieved the target serum urate level of ≤ 6.0 mg/dL at the final visit, and the serum urate levels at each time point. Blood pressure, eGFR, cystatin C, and urinary albumin levels (corrected for urinary creatinine level), were also analyzed to evaluate the efficacy of the study drug for blood pressure (BP) and renal function due to the effects of a decreased serum urate level.

2.4 Safety Evaluations

All adverse events (AEs) reported during the study were recorded, and those for which a causal relationship with topiroxostat could not be ruled out were defined as adverse drug reactions (ADRs). Administration was discontinued in patients who developed serious AEs. Prophylactic colchicine was prohibited during the topiroxostat administration period to evaluate the incidence rate of gouty arthritis.

2.5 Statistical Analyses

The efficacy and safety data were reported as mean ± standard deviation (SD). The differences in the variables were compared between the groups using paired *t* test with *p* value, unless stated otherwise. The significance level was set at 5% (two-sided).

The efficacy was evaluated in the full analysis set (FAS). Summary statistics and two-sided 95% confidence intervals (CIs) of the means were obtained. The same analyses were applied by stratification by the topiroxostat dosage at the final visit (120 mg, 160 mg, ≥ 200 mg, or others).

The achievement rate for the target serum urate level after 18 weeks of treatment or on the final visit were calculated as follows:

$$\text{Achievement rate (\%)} = [(\text{number of patients who achieved the target urate level of} \leq 6.0\,\text{mg/dL} / \text{number of patients in the analysis set}) \times 100.$$

The cumulative achievement rate was also calculated, with the assumption of monotonicity in the dose–response relationship. Calculation of the cumulative achievement rate and the two-sided 95% CIs was stratified by the topiroxostat dosage on the final visit (120 mg, 160 mg, 200 mg, or others).

As for the eGFR, cystatin C and urinary albumin (corrected for urinary creatinine), summary statistics and two-sided 95% CIs were calculated, and stratification by the topiroxostat dosage at the final visit (120 mg, 160 mg, ≥ 200 mg, or others) was applied to the same analyses. Natural logarithm transformation was performed for urinary albumin (corrected for urinary creatinine), and the geometric mean, the geometric SD and the two-sided 95% CIs were calculated using the converted values. The data were further analyzed using stratification by the topiroxostat dosage at the final visit (120 mg, 160 mg, ≥ 200 mg, or others). The ratios of the geometric means were calculated for the changes in the urinary albumin levels.

Safety evaluations were performed on the safety population (SP), which comprised all patients who received at least one dose of topiroxostat and had no critical GCP violations. The incidence rates and two-sided 95% CIs of AEs and ADRs, including and excluding gouty arthritis, were calculated. The same analyses were applied using stratification by the topiroxostat dosage at the final visit (120 mg, 160 mg, ≥ 200 mg, or others), causal relationship with topiroxostat and severity of AEs, and time points (at 4-week intervals from 2 to 58 weeks after the start of treatment, and after 58 weeks).

The incidence rates and two-sided 95% CIs of gouty arthritis were calculated. The incidence rates were further assessed using stratification by the topiroxostat dosage at the final visit (120 mg, 160 mg, ≥ 200 mg, or others) and time points (at 4-week intervals from 2 to 58 weeks after the start of treatment, and after 58 weeks).

For the changes in the clinical laboratory test values and vital signs, summary statistics were calculated at each time point (at 4-weeks intervals from 2 to 58 weeks after the start of treatment). The same analyses were applied using stratification by topiroxostat dosage at the final visit (120 mg, 160 mg, ≥ 200 mg, or others). Cross tabulation analysis was also conducted for changes in the clinical test values (interval scale data) at baseline and at each time point (at 4-week intervals from 2 to 58 weeks after the start of treatment). Statistical analyses on the data were conducted using Wilcoxon's signed-rank test.

The primary efficacy endpoint was analyzed as verification analysis in consideration of multiplicity, but the secondary endpoints were analyzed as exploratory analyses without consideration of multiplicity. Multiplicity was not considered for the safety analysis from the viewpoint of signal detection.

3 Results

3.1 Patient Details

A total of 150 patients were registered, 29 of whom were excluded for not meeting the inclusion criteria or for meeting the exclusion criteria, and the remaining 121 patients continued the study.

Three patients (2.5%) discontinued administration during initial period I at the initial dosage of 40 mg/day, and 118 patients (97.5%) completed initial period I. Three additional patients (2.5%) discontinued administration during initial period II at the initial dosage of 80 mg/day, and 115 patients (97.5%) completed initial period II. During maintenance period I (topiroxostat 120 mg/day), 5 patients (4.3%) discontinued administration, and 110 patients (95.7%) completed maintenance period I. During maintenance period II, there were 6 patients (5.5%) who discontinued administration (4 patients at 120 mg/day and 2 patients at 160 mg/day). A total of 104 patients (94.5%) completed maintenance period II at topiroxostat dosages of 120 mg/day in 75 patients, 160 mg/day in 16 patients, and ≥ 200 mg/day in 13 patients at the final visit.

FAS and SP included 121 patients at topiroxostat dosages of 120 mg/day in 84 patients, 160 mg/day in 18 patients, ≥ 200 mg/day in 13 patients, and other dosages in 6 patients at the final visit.

3.2 Patient Characteristics

Patient baseline characteristics are summarized in Table 1. The 121 patients constituting the FAS were 117 males (96.7%) and 4 females (3.3%). Patient age was 53.3 ± 12.2 years (mean ± SD), and body weight was 75.04 ± 13.02 kg. Of 121 patients in the FAS and SP, 85 patients (70.2%) had a history of treatment for hyperuricemia and 36 (29.8%) had no history of treatment. The serum urate level at baseline was 8.71 ± 1.18 mg/dL. As for the classification of hyperuricemia, the major type was "decreased excretion of uric acid", which was reported in 86 patients (71.1%). At baseline, eGFR level was 74.73 ± 16.46 mL/min/1.73 m^2, cystatin C was 0.757 ± 0.153 mg/L, and urinary albumin was 78.89 ± 267.72 mg/g·Cr. The same characteristics applied to 121 patients in the SP.

3.3 Efficacy

The results of the primary efficacy endpoint are shown in Table 2. Topiroxostat showed significant effects on the serum urate-lowering rate at the final visit (38.44 ± 13.34%, $n = 121$) ($p < 0.0001$) relative to the baseline level (primary

Table 1 Patient baseline characteristics (full analysis set)

Characteristic	*n* (%)				
	Total	Topiroxostat dosage at the final visit			
		120 mg	160 mg	≥ 200 mg	Other[a]
Number of patients	121	84	18	13	6
Sex					
Male	117 (96.7)	81 (96.4)	18 (100.0)	12 (92.3)	6 (100.0)
Female	4 (3.3)	3 (3.6)	0 (0.0)	1 (7.7)	0 (0.0)
Age (years)					
Mean ± SD	53.3 ± 12.2	54.3 ± 12.0	50.6 ± 12.1	50.7 ± 12.9	53.3 ± 15.1
Height (cm)					
Mean ± SD	168.01 ± 6.56	167.24 ± 6.03	168.81 ± 7.47	171.18 ± 7.82	169.53 ± 7.22
Body weight (kg)					
Mean ± SD	75.04 ± 13.02	73.50 ± 13.07	82.05 ± 14.06	76.42 ± 11.52	72.50 ± 3.44
Duration of hyperuricemia (years)					
Mean ± SD	8.57 ± 9.19	7.58 ± 7.82	9.22 ± 8.35	12.08 ± 10.36	12.87 ± 21.06
< 5.0	56 (46.3)	40 (47.6)	8 (44.4)	5 (38.5)	3 (50.0)
≥ 5.0 to < 15.0	43 (35.5)	32 (38.1)	5 (27.8)	4 (30.8)	2 (33.3)
≥ 15.0	22 (18.2)	12 (14.3)	5 (27.8)	4 (30.8)	1 (16.7)
History of treatment for hyperuricemia					
No	36 (29.8)	30 (35.7)	4 (22.2)	0 (0.0)	2 (33.3)
Yes	85 (70.2)	54 (64.3)	14 (77.8)	13 (100.0)	4 (66.7)
Serum urate at baseline (mg/dL)					
Mean ± SD	8.71 ± 1.18	8.32 ± 0.86	9.54 ± 1.20	10.22 ± 1.36	8.35 ± 0.99
≥ 7.0 to < 8.0	34 (28.1)	30 (35.7)	2 (11.1)	0 (0.0)	2 (33.3)
≥ 8.0 to < 9.0	47 (38.8)	39 (46.4)	3 (16.7)	3 (23.1)	2 (33.3)
≥ 9.0 to < 10.0	25 (20.7)	11 (13.1)	8 (44.4)	4 (30.8)	2 (33.3)
≥ 10.0	15 (12.4)	4 (4.8)	5 (27.8)	6 (46.2)	0 (0.0)
Disease classification					
Overproduction	23 (19.0)	19 (22.6)	2 (11.1)	2 (15.4)	0 (0.0)
Underexcretion	86 (71.1)	56 (66.7)	14 (77.8)	10 (76.9)	6 (100.0)
Mixed	3 (2.5)	1 (1.2)	1 (5.6)	1 (7.7)	0 (0.0)
Normal	3 (2.5)	2 (2.4)	1 (5.6)	0 (0.0)	0 (0.0)
Not evaluable	6 (5.0)	6 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)
History of gouty arthritis					
No	30 (24.8)	25 (29.8)	3 (16.7)	1 (7.7)	1 (16.7)
Yes	91 (75.2)	59 (70.2)	15 (83.3)	12 (92.3)	5 (83.3)
Gout nodules					
No	119 (98.3)	84 (100.0)	18 (100.0)	12 (92.3)	5 (83.3)
Yes	2 (1.7)	0 (0.0)	0 (0.0)	1 (7.7)	1 (16.7)
eGFR at baseline (mL/min/1.73 m^2)					
Mean ± SD	74.73 ± 16.46	73.80 ± 14.50	77.02 ± 16.71	73.37 ± 23.52	83.88 ± 24.50
≥ 30 to < 60	17 (14.0)	10 (11.9)	2 (11.1)	4 (30.8)	1 (16.7)
≥ 60 to < 90	86 (71.1)	64 (76.2)	13 (72.2)	7 (53.8)	2 (33.3)
≥ 90	18 (14.9)	10 (11.9)	3 (16.7)	2 (15.4)	3 (50.0)
Cystatin C, at baseline (mg/L)					
Mean ± SD	0.757 ± 0.153	0.755 ± 0.154	0.713 ± 0.091	0.812 ± 0.203	0.797 ± 0.159
Urinary albumin at baseline (mg/g·Cr)					
Geometric mean	17.59	17.76	22.02	14.31	12.24
95% CI	13.85, 22.33	13.44, 23.45	9.95, 48.71	5.78, 35.43	5.82, 25.72

Values are expressed as mean ± SD or *n* (%)

eGFR (mL/min/1.73 m^2) = 194 × Serum creatinine$^{-1.094}$ × Age$^{-0.287}$ × 0.739 (if female)

CI confidence interval, *eGFR* estimate glomerular filtration rate, *SD* standard deviation

[a]40 mg or 80 mg

Table 2 Serum urate-lowering rate at the final visit relative to the baseline level

Number of patients	Mean	SD	Minimum	Median	Maximum	95% CI	Paired *t* test
121	38.44	13.34	− 1.4	40.24	67.9	36.04, 40.84	$p < 0.0001$

CI confidence interval, *SD* standard deviation

endpoint). Significant reductions in the serum urate-lowering rates, by topiroxostat dosage at the final visit, were also found with 120 mg topiroxostat (38.60 ± 13.08%, $n = 84$), 160 mg (42.60 ± 12.51%, $n = 18$), and ≥ 200 mg (40.88 ± 8.89%, $n = 13$) ($p < 0.0001$ in all cases). In patients who received 160 mg topiroxostat at the final visit, the serum urate-lowering rate after 22 weeks of treatment was 11.29 ± 19.45% ($n = 18$), that after 30 weeks of treatment was 15.26 ± 10.93% ($n = 18$), and that after 58 weeks of treatment was 13.83 ± 16.03% ($n = 16$), relative to that after 18 weeks of treatment at which the dosage was increased from the maintenance dosage (120 mg/day). In patients treated with ≥ 200 mg topiroxostat at the final visit, the serum urate-lowering rate after 22 weeks of treatment relative to that after 18 weeks of treatment was 3.25 ± 19.50% ($n = 13$) and that after 30 weeks of treatment relative to that after 18 weeks of treatment was 1.87 ± 14.35% ($n = 13$), and that after 58 weeks of treatment relative to that after 30 weeks of treatment was 6.46 ± 15.13% ($n = 13$).

A significant change from baseline in the serum urate level was found at the final visit (− 3.39 ± 1.36 mg/dL, $n = 121$, $p < 0.0001$). Changes in the serum urate levels at the final visit by topiroxostat dosage were − 3.23 ± 1.18 mg/dL ($n = 84$) with 120 mg, − 4.14 ± 1.55 mg/dL ($n = 18$) with 160 mg, and − 4.22 ± 1.27 mg/dL ($n = 13$) with ≥ 200 mg ($p < 0.0001$ in all cases). In patients who received 160 mg topiroxostat at the final visit, the change in the serum urate level after 22 weeks of treatment relative to that after 18 weeks of treatment was − 0.88 ± 1.11 mg/dL ($n = 18$, $p = 0.0036$), the change after 30 weeks of treatment was − 1.06 ± 0.69 mg/dL ($n = 18$, $p < 0.0001$), and the change after 58 weeks of treatment was − 0.98 ± 1.07 mg/dL ($n = 16$, $p = 0.0023$). In patients treated with ≥ 200 mg topiroxostat at the final visit, no significant differences were found in changes in the serum urate levels after 22 weeks of treatment (− 0.38 ± 1.18 mg/dL, $n = 13$) and after 30 weeks of treatment (− 0.30 ± 1.16 mg/dL, $n = 13$) relative to that after 18 weeks of treatment, and after 58 weeks of treatment (− 0.47 ± 1.01 mg/dL, $n = 13$) relative to that after 30 weeks of treatment.

Patients who achieved the target serum urate level of ≤ 6.0 mg/dL after 18 weeks of treatment and at the final visit were 70.0% (77/110 patients) and 71.9% (87/121 patients), respectively. Cumulative achievement rates at the final visit by topiroxostat dosage were 57.9% (70/121 patients) of patients with ≤ 120 mg, 67.8% (82/121 patients) with ≤ 160 mg, and 71.9% (87/121 patients) with all dosages.

Changes in the serum urate levels during the administration of topiroxostat by the maintenance dosage (120 mg, 160 mg, and total) are presented in Fig. 2. The serum urate levels at baseline in patients, who received 120 mg, 160 mg, and ≥ 200 mg topiroxostat at the final visit were 8.32 ± 0.86 mg/dL, 9.54 ± 1.20 mg/dL, and 10.22 ± 1.36 mg/dL, respectively, which decreased to 5.09 ± 1.11 mg/dL, 5.40 ± 0.98 mg/dL, and 5.99 ± 0.89 mg/dL, respectively, by the time of the final visit.

At the final visit, diastolic BP (− 2.2 ± 11.4 mmHg, $n = 119$, $p = 0.0391$) and mean BP (− 2.43 ± 12.21 mmHg,

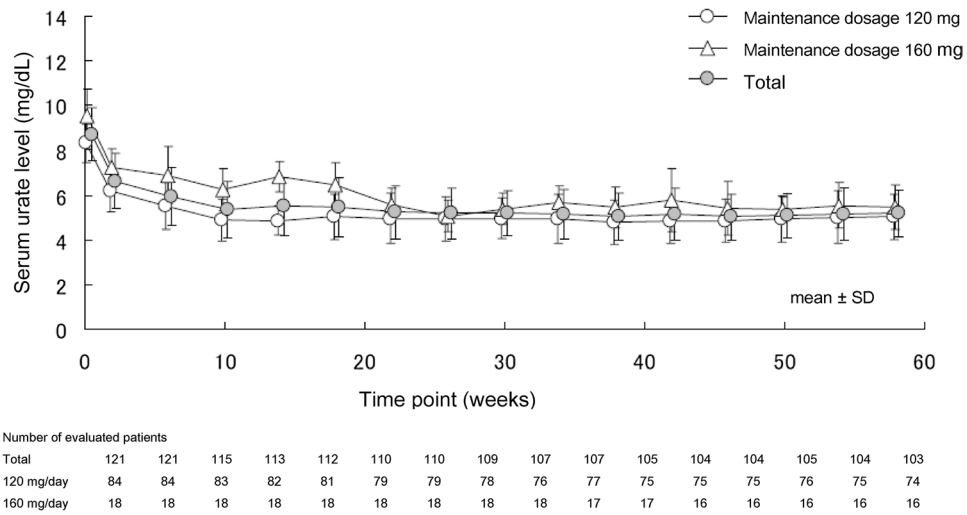

Fig. 2 Changes in the serum urate levels (FAS). *FAS* full analysis set, *SD* standard deviation. Values are expressed as mean ± SD

$n=119$, $p=0.0315$) were significantly decreased. Significant reductions in the systolic ($p=0.0189$), diastolic ($p=0.0178$), and mean BP ($p=0.0109$) in patients who received 120 mg topiroxostat at the final visit were also found (in all cases $n=84$).

The eGFR levels after 30 weeks of treatment (1.13 ± 7.41 mL/min/1.73 m^2, $n=107$) and at the final visit (0.47 ± 7.27 mL/min/1.73 m^2, $n=118$) had not changed significantly from the baseline levels.

The changes in the cystatin C levels after 30 weeks of treatment (0.046 ± 0.074 mg/L, $n=107$) and at the final visit (0.082 ± 0.079 mg/L, $n=118$) were significant ($p<0.0001$ in both cases). At the final visit, the changes in the cystatin C levels by the topiroxostat dosage at the final visit were 0.089 ± 0.081 mg/L with 120 mg ($n=82$, $p<0.0001$), 0.062 ± 0.055 mg/L with 160 mg ($n=18$, $p=0.0001$), and 0.091 ± 0.094 mg/L with ≥ 200 mg ($n=13$, $p=0.0045$).

The changes in the urinary albumin levels (difference between the baseline value and the value at each time point after logarithmic transformation), corrected for urinary creatinine level, after 30 weeks of treatment, after 58 weeks of treatment, and at the final visit (ratio of geometric mean) were 0.997 ($n=107$), 0.753 ($n=103$), and 0.794 ($n=118$), respectively; and significant reduction in the urinary albumin level was observed after 58 weeks of treatment ($p<0.0001$) and the final visit ($p=0.0001$). When the changes in the urinary albumin level (difference between the baseline value and the value at each time point after logarithmic transformation) were stratified by the topiroxostat dosage at the final visit, and significant reductions were found with 120 mg ($p=0.0006$) and ≥ 200 mg ($p=0.0025$) after 58 weeks of treatment, and 120 mg ($p=0.0005$) and ≥ 200 mg ($p=0.0025$) at the final visit (Table 3).

3.4 Safety

The incidence rates of AEs and ADRs were 97.5% (118/121 patients) and 67.8% (82/121 patients), respectively. The incidence rates of ADRs by the topiroxostat dosage at the final visit were 66.7% (56/84 patients) with 120 mg, 72.2% (13/18 patients) with 160 mg, 53.8% (7/13 patients) with ≥ 200 mg, and 100% (6/6 patients) with other dosages.

A list of ADRs reported in $\geq 5\%$ patients by PT in the SP is summarized in Table 4. The most frequently reported ADR by PT was α_1 microglobulin urine increased (27.3% of patients, 33/121 patients). Other major ADRs with $\geq 5\%$ incidence rates were β_2 microglobulin urine increased (20.7%, 25/121 patients), β-*N*-acetyl-D-glucosaminidase increased (19.8%, 24/121 patients), alanine aminotransferase increased (13.2%, 16/121 patients), β_2 microglobulin increased (11.6%, 14/121 patients), aspartate aminotransferase increased (9.9%, 12/121 patients), blood triglycerides increased (7.4%, 9/121 patients), γ-glutamyltransferase increased (7.4%, 9/121 patients), and albumin urine present (6.6%, 8/121 patients).

Gouty arthritis was reported in 9.1% (11/121) of patients and was determined to be an ADR in 5 patients (4.1%), 4 patients (4.8%) at 120 mg/day, 0 patients at 160 mg/day, and

Table 3 Changes in the urinary albumin levels after 30 weeks of treatment, after 58 weeks of treatment, and at the final visit from baseline (FAS)

Time point	Topiroxostat dosage at the final visit	*n*	Geometric mean[a]	Standard Deviation	95% CI[a]	Paired *t* test
After 30 weeks of treatment	Total	107	0.997	1.907	0.881, 1.128	$p=0.9582$
	120 mg	76	1.016	2.000	0.867, 1.190	$p=0.8461$
	160 mg	18	0.929	1.892	0.677, 1.276	$p=0.6327$
	≥ 200 mg	13	0.984	1.356	0.818, 1.183	$p=0.8513$
After 58 weeks of treatment	Total	103	0.753	1.873	0.666, 0.851	$p<0.0001$
	120 mg	74	0.767	1.900	0.661, 0.890	$p=0.0006$
	160 mg	16	0.759	2.095	0.512, 1.126	$p=0.1565$
	≥ 200 mg	13	0.672	1.459	0.534, 0.844	$p=0.0025$
Final visit	Total	118	0.794	1.921	0.705, 0.894	$p=0.0001$
	120 mg	82	0.776	1.894	0.675, 0.893	$p=0.0005$
	160 mg	18	0.792	2.034	0.556, 1.127	$p=0.1806$
	≥ 200 mg	13	0.672	1.459	0.534, 0.844	$p=0.0025$
	Other	5	1.782	2.326	0.624, 5.083	$p=0.2009$

Urinary albumin levels were corrected by urinary creatinine levels

Changes were estimated by the difference between the baseline value and the value at each time point after logarithmic transformation

CI confidence interval, *FAS* full analysis set

[a]Ratio of geometric means

Table 4 Adverse drug reactions that occurred in ≥ 5% of patients

System organ class/preferred term	Topiroxostat dosage at the final visit				
	Total	120 mg	160 mg	≥ 200 mg	Other
Number of patients	121	84	18	13	6
Adverse drug reactions	82 (67.8)	56 (66.7)	13 (72.2)	7 (53.8)	6 (100.0)
Musculoskeletal and connective tissue disorders	9 (7.4)	7 (8.3)	0 (0.0)	2 (15.4)	0 (0.0)
Gouty arthritis	5 (4.1)	4 (4.8)	0 (0.0)	1 (7.7)	0 (0.0)
Investigations	76 (62.8)	53 (63.1)	12 (66.7)	6 (46.2)	5 (83.3)
Alanine aminotransferase increased	16 (13.2)	12 (14.3)	3 (16.7)	0 (0.0)	1 (16.7)
Albumin urine present	8 (6.6)	5 (6.0)	2 (11.1)	0 (0.0)	1 (16.7)
Aspartate aminotransferase increased	12 (9.9)	10 (11.9)	2 (11.1)	0 (0.0)	0 (0.0)
Beta 2 microglobulin increased	14 (11.6)	12 (14.3)	1 (5.6)	1 (7.7)	0 (0.0)
Beta 2 microglobulin urine increased	25 (20.7)	16 (19.0)	4 (22.2)	4 (30.8)	1 (16.7)
Beta-*N*-acetyl-D-glucosaminidase increased	24 (19.8)	20 (23.8)	2 (11.1)	1 (7.7)	1 (16.7)
Blood triglycerides increased	9 (7.4)	6 (7.1)	1 (5.6)	2 (15.4)	0 (0.0)
Gamma-glutamyltransferase increased	9 (7.4)	7 (8.3)	1 (5.6)	0 (0.0)	1 (16.7)
Alpha 1 microglobulin urine increased	33 (27.3)	21 (25.0)	8 (44.4)	2 (15.4)	2 (33.3)

Values are expressed as *n* (%)

1 patient (7.7%) at ≥ 200 mg/day (Table 4). Gouty arthritis was reported only after 2 weeks of treatment [3/121 patients (2.5%)], after 6 weeks of treatment [1/118 patients (0.8%)], and after 14 weeks of treatment [3/113 patients (2.7%)], but not at other time points.

One patient died of bile duct cancer, which did not have a causal relationship with topiroxostat. Eight other serious AEs were reported in 9 patients, of which 3 AEs in 2 patients (aortic aneurysm, coronary artery stenosis, and cardiac failure congestive) were considered possibly related to topiroxostat. Eleven patients discontinued administration due to the AEs.

4 Discussion and Conclusion

In this study, the sustained efficacy, development of drug-resistance, and safety of long-term topiroxostat administration were studied in hyperuricemic patients with or without gout. The initial dosage of oral topiroxostat was 40 mg/day for 2 weeks and was increased to 80 mg/day over the following 4 weeks and to 120 mg/day in the 52-week maintenance period. The dosage during the maintenance period was adjusted at 40-mg increments up to 240 mg, if the serum urate level was > 6.0 mg/day and the patient tolerated it. The results indicated that the serum urate levels and the serum urate-lowering rate remained constant for a long time, suggesting that drug-resistance to topiroxostat was unlikely to develop.

Prevention of gouty arthritis is an important treatment goal of serum urate-lowering therapy [2–5]. However, treatment with selective xanthine oxidoreductase inhibitors, especially at an early phase [20], may accelerate the development of gouty arthritis through a rapid reduction in the serum urate level. Therefore, we evaluated the risk of developing gouty arthritis during topiroxostat administration by the dose-escalation method. This method was recommended in Japan because it may prevent the development of gouty arthritis from rapid reduction in serum urate levels during treatment for hyperuricemia.

A 52-week study on the long-term administration of febuxostat, which is another XO inhibitor, showed that gouty arthritis developed in 27 patients (20.6%, 52 events) in the 40 mg group and in 10 patients (25.0%, 26 events) in the 60 mg group [21]. Moreover, that study described that the overall incidence of gouty arthritis was only 6.5%, even during the period when the dose was increased to 40 mg from week 4 to week 8.

In the initial administration period in this study, gouty arthritis had a low incidence rate, which further declined during the long-term administration period. These results implied that gouty arthritis did not last for a long time, and gradually disappeared. Therefore, topiroxostat might be more beneficial in hyperuricemic patients who experience gouty arthritis, as supported by the relatively low incidence (Table 4).

Additional analyses revealed that topiroxostat use was associated with a significant reduction in urinary albumin on the final visit. Although the relationships of topiroxostat with reduction in urinary albumin and the small but significant lowering BP are unknown, topiroxostat may have a renoprotective effect on hyperuricemic patients.

In conclusion, the efficacy and safety of oral topiroxostat administration, at an initial dosage of 40–80 mg/

day and at a maintenance dosage of 120 mg/day for up to 58 weeks, were verified. Stepwise increments were also found to be safe.

Acknowledgements We are grateful to the investigators, local study coordinators, and the patients for their valuable contributions to these studies.

Compliance with Ethical Standards

Conflict of interest TH has received consultant fees and/or speakers' honoraria from Fuji Yakuhin Co., Ltd., the manufacturer of topiroxostat, and/or Sanwa Kagaku Kenkyusho Co., Ltd. TI and TO are employees of Fuji Yakuhin Co., Ltd. RS and YO are employees of Sanwa Kagaku Kenkyusho Co., Ltd.

Ethics Approval This study and its protocol were approved by the following local IRBs of participating sites: Chubu Rosai Hospital IRB (02/22/2010), IRB Of Kouseikai Sone Clinic (02/24/2010), Abe Clinic IRB (02/24/2010), Gifu Prefectural General Medical Center IRB (03/17/2010), Social Medical Corporation the Chiyukai foundation Fukuoka Wajiro Hospital IRB (03/18/2010). This study was conducted in compliance with the Helsinki Declaration, Good Clinical Practice guidelines, and other relevant laws and regulations.

Funding This study was funded by Fuji Yakuhin Co., Ltd. and Sanwa Kagaku Kenkyusho Co., Ltd.

Informed Consent All patients provided written informed consent before initiation of the study.

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