Clinical efficacy and safety of topiroxostat in Japanese male hyperuricemic patients with or without gout: an exploratory, phase 2a, multicentre, randomized, double-blind, placebo-controlled study

T. Hosoya* MD PhD, T. Sasaki† PhD, H. Hashimoto‡ PhD, R. Sakamoto‡ MSc and T. Ohashi† PhD

*Department of Pathophysiology and Therapy in Chronic Kidney Disease, Jikei University School of Medicine, Tokyo, †Medical R&D Division, Fuji Yakuhin Co., Ltd., Saitama, and ‡Drug Development Center, Surawa Kagaku Kenkyusho Co., Ltd., Aichi, Japan

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SUMMARY

What is known and objective: In Japan, although topiroxostat, a selective xanthine oxidoreductase inhibitor, has been used for the treatment of patients with hyperuricemia including gout, no published randomized controlled studies evaluating the dose-dependent relationship with respect to the serum urate-lowering efficacy have been reported. The aim of this study was to evaluate the dose-dependent relationship with serum urate-lowering efficacy and safety of topiroxostat in Japanese hyperuricemic patients including gout.

Methods: We conducted an exploratory, phase 2a, multicentre, randomized, double-blind, 8-week, placebo-controlled study in Japanese hyperuricemic patients with or without gout. The study arms were placebo and topiroxostat 40, 60, 80 or 120 mg/day. The primary efficacy endpoint was the per cent change in serum urate level from baseline to the final visit.

Results and discussion: One hundred and eighty-seven eligible patients were randomized and 186 received at least one dose of the study drug. The study results demonstrated a dose-dependent serum urate reduction effect ranging from 40 to 120 mg/day (P < 0.001, Jonckheere–Terpstra test). The mean per cent change in serum urate level from baseline at the final visit was ~30.8% in the 120-mg group and 1.6% with placebo, with a between-group difference of ~32.4% (95% confidence interval, −38.9% to −25.9%; P < 0.001). Incidences of overall adverse events (AEs) in the topiroxostat groups were comparable to those in the placebo group; however, the incidence of AEs in the 120-mg group was statistically lower than that in the placebo group. The incidences of gouty arthritis were not statistically but numerically higher in the topiroxostat 80- and 120-mg groups.

What is new and conclusions: A dose-dependent serum urate-lowering efficacy of topiroxostat was observed in Japanese hyperuricemic male patients with or without gout. Further clinical studies aimed at evaluating the long-term safety and clinical efficacy are warranted.

WHAT IS KNOWN AND OBJECTIVE

Hyperuricemia (defined as the serum urate level >416.4 μmol/L [or 7.0 mg/dL] in Japan) is a causative factor of urate deposition diseases (e.g. uricolithiasis and gouty arthritis). From the standpoint of preventing gout, the primary goal of treating hyperuricemia is to reduce the serum urate level and maintain it at ≤356.9 μmol/L (or 6.0 mg/dL), and at this level, urate crystal deposition is reversed.1,2

Meanwhile, among the population of asymptomatic hyperuricemia, the high serum urate level population (≥475.8 μmol/L) showed higher incidence of gouty arthritis.3,4 Some clinical studies suggested cardio or renal protective action of urate-lowering therapy.5-7 In addition, epidemiological studies suggested hyperuricemia is considered as independent risk or predictive factor for cardiovascular disease.8-10 In consideration of these evidences, asymptomatic hyperuricemia (serum urate level ≥475.8 μmol/L) with renal disease, hypertension, metabolic disease or ischaemic heart disease can be considered as an indication of drug therapy in Japanese guideline for the management of hyperuricemia and gout. This therapeutic policy is significantly different from other countries.

Two xanthine oxidoreductase (XOR) inhibitors, namely allopurinol and febuxostat, are widely used around the world as urate-lowering agents. Allopurinol is generally safe and effective, although rarely it induces severe allopurinol hypersensitivity syndrome (AHS).11 To avoid the onset of AHS, dose reduction of allopurinol is recommended in patients with renal impairment.12

Another XOR inhibitor, febuxostat, showed a strong serum urate reduction effect compared with allopurinol.13

In Japan, topiroxostat (formerly known as FYX-051) is another novel, orally administered, non-purine-type XOR inhibitor that is recently approved for the treatment of patients with hyperuricemia including gout.14,15 In contrast to allopurinol, the pharmacokinetics of topiroxostat is not affected by the renal function.16 Compared with febuxostat, which has active oxidative metabolites, the major metabolites of topiroxostat (N-glucuronide and N-oxide form) were generally inactive to XOR (IC50 > 10 μmol/L), and the urinary excretion rate of topiroxostat is less than 0.1% of the dose in patients with moderate renal impairment.17,18 In addition, topiroxostat has also been shown to reduce the serum urate and urinary albumin excretion in Japanese hyperuricemic patients with moderately impaired renal function.19

The reduction effect of urinary albumin excretion of topiroxostat in hyperuricemia with diabetic nephropathy has currently been
explored (UPWARD; NCT02327754). However, these studies did not assess the dose-dependent serum urate reduction effect of topiroxostat in Japanese hyperuricemic patients. To evaluate the serum urate-lowering efficacy, dose-dependent relationship and safety of topiroxostat in Japanese hyperuricemic patients with or without gout, we conducted an exploratory phase IIa study in Japan.

METHODS

Study design

This exploratory study of FYX-051 in hyperuricemic patients with or without gout was a phase 2a, multicentre, randomized, double-blind, 8-week, placebo-controlled study. Ten clinical institutions in Japan participated in the study (Tokyo Women’s Medical University Medical Center East, Takeuchi Hospital, Suzuki Hospital, Keigui Hospital, Miyazono Naika Clinic, Akasaka Chuou Clinic, Toranomon Shinryojiyo, Kamiyoga Setagaya Street Clinic, Ryougoku East Gate Clinic and Shinjuku Oak Tower Clinic). The study schema is shown in Fig. 1. The study was approved by the institutional review board of each of the participating institutions in Japan. The current study was conducted in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines and other applicable regulatory requirements. A written informed consent was obtained from all the participating patients prior to the initiation of any study-related procedures. The clinical trial information of the study has been registered with the Japan Pharmaceutical Information Center (JAPIC) (Registration number: JapicCTI-101315). No interim analyses were performed.

Fig. 2. Flow diagram of the study.

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Inclusion and exclusion criteria

The inclusion criteria were as follows: (i) the presence of hyperuricemia (serum urate level ≥475.8 μmol/L), (ii) Japanese patient and (iii) age 20–64 years on the day of submission of the written consent for the participation in the study (due to lack of information about pharmacokinetics of topiroxostat in patients over the age of 65 years at the time of the study).

The exclusion criteria were as follows: an attack of gouty arthritis within 2 weeks prior to the first day of the study drug administration; hyperuricemia secondary to certain disorders; diabetes (fasting plasma glucose level ≥7.0 mmol/L or casual blood glucose level ≥11.1 mmol/L); impaired renal function (serum creatinine level ≥132.6 μmol/L); hepatic function impairment (serum alanine aminotransferase [ALT] ≥100 IU/L); severe hypertension (systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg); use of urate-lowering agents, azathioprine, 6-mercaptopurine, theophylline, the study drug other than topiroxostat or agents potentially affecting the serum urate level from the first day of the study drug administration; and the presence of any other clinically significant medical condition that could potentially preclude the participation in this study. If patients had been treated with any urate-lowering agents or agents affecting the serum urate level prior to their enrolment in the study, they were entered in the study only after a washout period of more than 2 weeks.

Randomization and Blinding

A computer-generated dynamic allocation sequence was prepared by the independent organization and was not accessible to anyone else involved in the study until the time of unblinding. The balancing factors for the randomization were ‘study sites’, ‘serum urate level at the baseline’, ‘classification of hyperuricemia’ and ‘history of gouty arthritis’. As for the classification of hyperuricemia, based on uric acid measurement in the 60-minute urine collection during the run-in period, we classified patients into the following four types: (i) patients with urinary excretion of uric acid (EUA, [mg/kg/h]) > 0.51 and uric acid clearance (CUA, [mL/min]) ≥ 7.2 were defined as ‘urate overproduction type’, (ii) patients with EUA < 0.48 or CUA < 7.2 were defined as ‘urate underexcretion type’, (iii) patients with EUA > 0.51 and CUA < 7.2 were defined as ‘combined type’, and patients with 0.48 ≤ EUA ≤ 0.51 and CUA ≥ 7.2 were defined as ‘normal type’. The independent organization concealed the allocation information until the completion of study data assessment of all patients. The serum urate levels after the administration of the study drug to each patient were concealed from all investigators, staff and patients throughout the study.

Intervention and follow-up

Patients were randomly assigned to either placebo or topiroxostat 40, 60, 80 or 120 mg daily (ratio 1 : 1 : 1 : 1). We used the dose titration method to minimize the risk of gouty arthritis arising in association with rapid serum urate reduction.3 The treatment period was 8 weeks, and patients were followed up every 2 weeks at their clinical institution after randomization.

Endpoints

The primary efficacy endpoint was the per cent change in serum urate level from baseline to the final visit. The secondary efficacy endpoint was the percentage of patients with serum urate level ≤ 356.9 μmol/L at the final visit. Serum urate levels were measured by the Uricase F-DAOS method (Wako Pure Chemical Industries, Japan).

### Table 1. Baseline characteristics (full analysis set)

|                        | Placebo       | 40 mg         | 60 mg         | 80 mg         | 120 mg        | P value |
|------------------------|---------------|---------------|---------------|---------------|---------------|---------|
| Male/Female            | 36/0          | 38/0          | 37/0          | 38/0          | 37/0          | –       |
| Age (year)             | 45.7 ± 9.8    | 45.8 ± 10.9   | 45.2 ± 7.9    | 44.7 ± 9.7    | 46.3 ± 9.0    | 0.960b  |
| BMI (kg/m²)            | 25.7 ± 3.8    | 26.1 ± 3.6    | 26.7 ± 4.1    | 25.9 ± 4.0    | 26.1 ± 2.8    | 0.794b  |
| Duration of hyperuricemia (year) | 7.5 ± 6.8 | 7.6 ± 7.1    | 6.6 ± 6.9    | 6.8 ± 6.6    | 5.7 ± 6.4    | 0.757b  |
| Serum urate (μmol/L)   | 542.9 ± 56.0  | 531.6 ± 66.5  | 548.5 ± 62.1  | 550.0 ± 66.6  | 544.3 ± 58.5  | 0.970b  |
| eGFR (mL/min/1.73 m²)  | 81.1 ± 16.5   | 77.0 ± 11.1   | 78.0 ± 13.3   | 74.8 ± 12.8   | 76.9 ± 13.8   | 0.378b  |
| History of gouty arthritis, n (%) | 23 (63.9) | 26 (68.4) | 25 (67.6) | 25 (65.8) | 25 (67.6) | 0.994a  |
| Existence of gouty tophus, n (%) | 1 (2.8) | 0 (0.0) | 0 (0.0) | 2 (5.3) | 1 (2.7) | 0.475a  |
| History of gout, n (%)  | 9 (25.0)      | 8 (21.1)      | 7 (18.9)      | 10 (26.3)     | 13 (35.1)     | 0.545a  |
| Drinking habit, n (%)  | 24 (66.7)     | 16 (42.1)     | 25 (67.6)     | 24 (63.2)     | 30 (81.1)     | 0.012a  |
| History of drug treatment for hyperuricemia, n (%) | 26 (72.2) | 23 (78.7) | 28 (75.7) | 30 (78.9) | 24 (64.9%) | 0.720a  |

| Classification of hyperuricemia, n (%) | | | | | |
| Urate overproduction type | 7 (19.4) | 9 (23.7) | 7 (18.9) | 9 (23.7) | 9 (23.7) | 0.909a |
| Urate underexcretion type | 25 (69.4) | 25 (65.8) | 24 (64.9) | 24 (63.2) | 25 (67.6) | |
| Combined type | 4 (11.1) | 4 (10.5) | 4 (10.8) | 4 (10.5) | 3 (8.1) | |
| Normal type | 0 (0.0) | 0 (0.0) | 2 (5.4) | 1 (2.6) | 0 (0.0) | |

Values are expressed as mean ± standard deviation or n (%). Statistical significance was defined as a two-tailed P value of less than 0.15.

BMI, body mass index; eGFR, estimated glomerular filtration rate.

*χ²-test; ANOVA.

eGFR (mL/min/1.73 m²) = 194 × Serum creatinine^{-1.044} × Age^{-0.287} × 0.739 (if female).

Definition of drinking habit: consumption of alcohol on more than 3 days of the week and consumption of more than 500 mL of beer or 60 mL of whisky in 1 day.
Exploratory clinical study of topiroxostat

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Results of primary and secondary efficacy endpoints (full analysis set)

Table 2. Results of primary and secondary efficacy endpoints (full analysis set)

| End point | Placebo | 40 mg | 60 mg | 80 mg | 120 mg |
|-----------|---------|-------|-------|-------|--------|
| Primary efficacy endpoint: Percentage change in serum urate level from baseline to the final visit | 1.6 ± 10.9% (67) | -2.5 (31.8 to 8.7) | -2.6 (31.7 to 8.6) | -3.2 (39.9 to 8.9) | -3.2 (39.9 to 8.9) |
| Difference between placebo and each treatment group | -0.001 | -0.001 | -0.001 | -0.001 | -0.001 |
| Secondary efficacy endpoints: Percentage of patients with serum urate level ≤356.0 mmol/L at the final visit | 0.35 (0.0 to 10.0) | 7.78 (0.4 to 36.0) | 8.72 (0.4 to 36.0) | 10.2 (0.4 to 36.0) | 16.37 (0.4 to 36.0) |
| P value | 0.004 | 0.024 | 0.014 | 0.001 | 0.001 |

95% confidence intervals of difference between groups and P values (placebo vs. each topiroxostat group) were adjusted by Dunnett–Hsu's method.

Fig. 3. Time course of the serum urate levels (full analysis set).

Safety evaluations

Any adverse events (AEs) and safety assessments conducted by the clinical investigators, including vital signs, 12-lead electrocardiography, clinical laboratory tests and clinical examinations, were recorded during the study. AEs were classified according to the system organ class and preferred term (MedDRA/® version 9.1; Japanese Maintenance Organization, Tokyo, Japan) and were evaluated in terms of their potential relationship with the study drug and severity. We did not permit colchicine prophylaxis throughout the study period. If gouty arthritis developed during the study period, the patients were treated with colchicine, non-steroidal anti-inflammatory drugs or corticosteroids at the discretion of the investigator. In addition, to evaluate the effect of topiroxostat on the renal function, we assessed the estimated glomerular filtration rate (eGFR) in each treatment group at each visit by post hoc analysis. The serum creatinine levels were measured by the enzymatic method (Wako Pure Chemical Industries, Ltd.). The measurement methods for each clinical item are listed in the Supplementary information.

Statistical analyses

We estimated that the per cent change in serum urate level from baseline to the final visit would be -35 ± 10%. We calculated that 34 patients per group were needed to estimate the width of the two-sided 95% confidence interval with ±3% accuracy. Taking into consideration the possible dropout of some patients, we set the number of patients in each group at 40.

Efficacy analyses were performed on the full analysis set comprising all the randomized patients who received at least one dose of the study drug and underwent serum urate measurement during at least one visit. To impute the missing value of serum urate levels, the modified last observation carried forward was used; if the serum urate data at week 8 were missed, the data at week 6 or week 4 were used as the final visit data. The approach was prespecified before the start of the study.

In the analyses of the primary efficacy endpoint, comparisons of the mean values between study groups were performed. Dunnett–Hsu’s method was used to adjust multiple comparisons.

The Jonckheere–Terpstra test was used to evaluate the dose dependency of primary efficacy endpoint, χ² test was used for
testing the secondary efficacy endpoint, and Bonferroni correction was used to avoid the multiplicity of testing. Cochran–Armitage test was used for the evaluation of dose dependency of the secondary efficacy endpoint. In addition, we performed a pre-specified subgroup analysis of the primary efficacy endpoint by the classification of hyperuricemia.

Safety analyses were performed on the safety population, which consisted of all the patients who took at least one dose of the study drug. The incidences of AEs were summarized in the number and proportion of patients.

The post hoc analysis of the change of eGFR at each visit was conducted in the full analysis set. The changes of eGFR at each visit were summarized. The analysis of covariance was used to compare the change of eGFR with baseline value as a covariate. Dunnett–Hsu’s method was used to adjust multiple comparisons.

Statistical analyses were performed using the Statistical Analysis System Release 8.2 (SAS Institute Inc., Cary, NC, USA). All values are expressed as mean ± standard deviation (SD) unless otherwise specified. The statistical significance was defined based on a two-tailed P value of less than 0.05. The statistical significance of between-group differences at the baseline was defined based on a two-tailed P value of less than 0.15.

RESULTS AND DISCUSSION

Patient flowcharts and baseline characteristics

The flow diagram of patients in the study is summarized in Fig. 2. Between March 2006 and October 2006, 270 patients were screened, 187 were randomized, 186 received at least one dose of the study drug, 7 of 186 did not complete the study (2 discontinued by AE (gouty arthritis), 2 withdrew consent, 2 lost to follow-up and 1 had other reason) and 179 completed the study. Among randomized 187 patients, one patient in 120-mg group withdrew the study before receiving the study drug (personal reason). Therefore, a total of 186 patients were included in the efficacy and safety analyses. The baseline characteristics were similar among five groups except for drinking habits (Table 1). All the patients were Japanese men. The mean age was 45.5 ± 9.4 years, the mean serum urate level was 547.8 ± 61.9 μmol/L, 66.7% had a history of gouty arthritis, 22.2% had gouty tophus, and 73.1% had the drug treatment for hyperuricemia. These baseline characteristics were comparable with other study in Japan.23

Efficacy

One patient in the placebo group, two in the 40-mg group, one in the 80-mg group and two in the 120-mg group withdrew the study before the week 4 visit. According to the prespecified statistical missing data management criterion, the serum urate data of these patients at week 2 were not included in the primary and secondary efficacy analyses.

The primary efficacy endpoint – the per cent change in serum urate level from baseline to the final visit – was significantly higher in the topiroxostat groups than in the placebo group, with a dose-dependent relationship (P < 0.001, Jonckheere–Terpstra test) (Table 2). The secondary efficacy endpoint was significantly higher in each of the topiroxostat groups than in the placebo group with dose-dependent relationship (P < 0.001, Cochran–Armitage test) (Table 2). The time course of the changes in serum urate levels is shown in Fig. 3. The subgroup analysis of the primary efficacy endpoint by the classification of hyperuricemia is shown in Table 3.

We showed, for the first time, the dose-dependent relationship with respect to the serum urate-lowering effect of topiroxostat in Japanese hyperuricemic patients with or without gout. Although topiroxostat demonstrated a significant dose-dependent serum urate level reduction in the study, the percentage of patients with serum urate level ≤356.9 μmol/L in topiroxostat group was less than 50%, even in the topiroxostat 120-mg group. It is not known exactly why, but this low achievement rates may be considered to be derived from a relatively high serum urate level and/or lack of doses of topiroxostat. In addition, this is not a comparative clinical trial with other urate-lowering agent; therefore, it is difficult to make a conclusion of this low achievement rate. To clarify the clinical position of topiroxostat, a comparative clinical trial with allopurinol or febuxostat is needed.

As a result of prespecified subgroup analysis by the classification of hyperuricemia, because topiroxostat showed numerically similar per cent change in serum urate level in 80- and 120-mg groups, topiroxostat may have serum urate-lowering efficacy beyond the classification of hyperuricemia. However, because the number of each subgroup was relatively small, further clinical trial is needed.

Safety

No serious AE was observed, and all the AEs were mild to moderate in severity. The frequently reported AEs (incidence ≥5%) are listed in Table 4. The AEs that were moderate in severity included gouty arthritis (one patient each in the placebo group and topiroxostat 60- and 120-mg groups and four patients in the topiroxostat 80-mg group) and dermatitis (one patient in the topiroxostat 40-mg group). The overall incidence rates of AEs were similar among all the study groups, except the 120-mg group. The overall incidence of AEs in the 120-mg group was significantly lower than that of placebo group (P = 0.021, χ² test), but the reasons are unknown. Further long-term studies are

Table 3. Subgroup analysis of per cent change in serum urate level from baseline to the final visit by the classification of hyperuricemia (full analysis set)

| Group                          | Placebo | 40 mg     | 60 mg     | 80 mg     | 120 mg    |
|-------------------------------|---------|-----------|-----------|-----------|-----------|
| Urate overproduction type     | 4.9 ± 7.1 (6) | −24.1 ± 7.1 (9) | −19.4 ± 11.1 (7) | −31.1 ± 11.4 (9) | −28.9 ± 10.4 (8) |
| Urate underexcretion type     | 0.4 ± 12.0 (25) | −24.3 ± 9.6 (24) | −21.4 ± 10.6 (24) | −28.8 ± 12.7 (23) | −31.7 ± 12.4 (24) |
| Combined type                 | 4.1 ± 6.4 (4) | −15.1 ± 14.5 (3) | −29.3 ± 8.9 (4) | −34.9 ± 11.3 (4) | −28.5 ± 18.7 (3) |
| Normal type                   | −(0)    | −(0)      | −31.9 ± 11.5 (2) | −29.1 (1) | −(0)      |

Values are expressed as mean ± standard deviation (no. of patients).
needed to obtain the additional safety information of topiroxostat.

The incidence of gouty arthritis in the topiroxostat 80- and the 120-mg groups was not significantly but numerically higher than that of placebo group ($P = 0.264, 0.145, \chi^2$ test) (Table 4). It is well known that rapid serum urate reduction often induces the onset of gouty arthritis, especially in the initial treatment phase. Therefore, the cause of 2- to 3-fold higher incidence of gouty arthritis in the 80- and 120-mg groups may be due to the rapid serum urate reduction by topiroxostat. In addition, for evaluating the risk of gouty arthritis events during the study, we did not permit the use of prophylactic treatments such as colchicine administration. This study design may also affect the numerically higher incidence of gouty arthritis in the topiroxostat group. Instead of restricted prophylactic treatments, we adopted the dose titration method, which is encouraged in Japan for minimizing the onset of gouty arthritis caused by rapid serum urate reduction during the treatment. A more gradual stepwise dose titration design to avoid rapid serum urate reduction may be needed.

The pharmacokinetics of topiroxostat is not affected by mild or moderate renal impairment, and dose adjustment is not indicated for such patients. Compared with allopurinol, this is a clinically significant difference. Therefore, topiroxostat can be potentially prescribed to patients with impaired renal function, and we assessed the influence of topiroxostat on renal function in this study.

As a result of post hoc analysis, topiroxostat at least did not reduce the eGFR (Table 5). The reason for the significant changes in eGFR in the topiroxostat groups (80 and 120 mg) compared with the placebo group is not clear. Although this result might come from unexpected differences in eGFR in placebo group, the finding seems to be considered having a value for further research for the following reasons. First, the function of XOR is not only producing urate but also producing reactive oxygen species, and xanthine oxidase impaired glomerular

Table 4. Summary of the adverse events (safety population)

|                  | Placebo  | 40 mg  | 60 mg  | 80 mg  | 120 mg |
|------------------|----------|--------|--------|--------|--------|
|                  | n = 36   | n = 38 | n = 37 | n = 38 | n = 37 |
| Any AEs           | 27 (75)  | 27 (71) | 28 (75) | 24 (63) | 18 (48) |
| Frequent AEs (%)  | 5%       | 5%     | 5%     | 5%     | 5%     |
| Stomatitis        | 2 (5.6)  | 0 (0)  | 1 (2.7) | 0 (0)  | 0 (0)  |
| Nasopharyngitis   | 6 (16.7) | 4 (10.5)| 3 (8.1)| 1 (2.6)| 1 (2.7)|
| ALT increased     | 2 (5.6)  | 2 (5.3)| 3 (8.1)| 3 (7.9)| 3 (8.1)|
| AST increased     | 0 (0)    | 3 (7.9)| 2 (5.4)| 2 (5.3)| 2 (5.4)|
| Urinary β2 microglobulin increased | 2 (5.6) | 1 (2.6) | 0 (0) | 0 (0) | 1 (2.7) |
| Urinary NAG increased | 6 (16.7) | 6 (15.8)| 5 (13.5) | 2 (5.3) | 2 (5.4) |
| Blood bilirubin increased | 0 (0) | 2 (5.3)| 1 (2.7)| 1 (2.6)| 2 (5.4)|
| Blood CKP increased | 3 (8.3)| 5 (13.2)| 4 (10.8)| 2 (5.3)| 2 (5.4)|
| Blood TG increased | 1 (2.8)| 1 (2.6)| 1 (2.7)| 3 (7.9)| 2 (5.4)|
| γ-GTP increased   | 0 (0)    | 2 (5.3)| 3 (8.1)| 1 (2.6)| 0 (0)  |
| Blood urine present | 0 (0) | 1 (2.6)| 0 (0) | 2 (5.3)| 0 (0)  |
| WBC count decreased | 0 (0) | 2 (5.3)| 1 (2.7)| 2 (5.3)| 1 (2.7)|
| Platelet count increased | 0 (0) | 0 (0) | 0 (0) | 2 (5.3)| 0 (0)  |
| Arthralgia        | 2 (5.6)  | 0 (0)  | 2 (5.4)| 0 (0)  | 0 (0)  |
| Gouty arthritis   | 2 (5.6)  | 1 (2.6)| 1 (2.7)| 5 (13.2)| 6 (16.2)|
| Headache          | 0 (0)    | 2 (5.3)| 0 (0)  | 0 (0)  | 0 (0)  |

Values are expressed in number of patients (percentage).
*AEs were defined as adverse events that occurred between the first day of dosing and the final visit.
+AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NAG, beta-N-acetyl-D-glucosaminidase; CKP, creatine phosphokinase; TG, triglyceride; GTP, glutamyltransferase; WBC, white blood cell.

Table 5. Post hoc analysis of the change of eGFR (full analysis set)

|          | Placebo  | 40 mg  | 60 mg  | 80 mg  | 120 mg |
|----------|----------|--------|--------|--------|--------|
| Week 2   | –2.63 ± 7.76 (36) | 0.52 ± 6.13 (38) | –0.85 ± 4.86 (37) | 0.28 ± 6.36 (38) | –0.39 ± 5.48 (37) |
| Week 4   | –3.80 ± 8.96 (35) | –0.73 ± 6.29 (37) | –0.89 ± 4.54 (37) | 0.40 ± 6.05 (37) | 0.52 ± 6.65 (36) |
| Week 8   | –3.00 ± 7.29 (35) | –0.67 ± 5.54 (36) | –0.68 ± 5.42 (37) | 1.10 ± 6.60 (36) | 2.83 ± 6.48 (35) |
| P value* (Week 8) | <0.001 | 0.390 | 0.370 | 0.035 |

Values are expressed as mean ± standard deviation (no. of patients).
*P values (placebo vs. each topiroxostat group at week 8) were adjusted by Dunnett-Hsu’s method.

eGFR (ml/min/1.73 m²) = 194 × Serum creatinine $^{-1.094}$ × Age$^{-0.205}$ × 0.739 (if female).23
eGFR, estimated glomerular filtration rate.
proteoglycans. Second, XOR inhibitors showed a significant improvement of GFR. Third, topiroxostat showed the protective effect on familial juvenile hyperuricemic nephropathy model and showed urinary albumin reduction in patients with stage 3 chronic kidney disease.

**Limitations of the study**

Some limitations of this study warrant mention. First, the study period was short, which may limit the estimation of the serum urate-lowering efficacy and the safety of topiroxostat. Second, due to the limited inclusion criteria of age (age 20–64 years), these study results do not contribute the estimation of serum urate-lowering efficacy of topiroxostat in patients whose age is greater or equal to 65 years. This study was conducted in Japanese male patients, limiting the generalizability of the results to other patient populations.

**WHAT IS NEW AND CONCLUSIONS**

The exploratory phase 2a study demonstrated a dose-dependent relationship with respect to the urate-lowering efficacy of the drug in Japanese hyperuricemic male patients with or without gout. Further clinical studies aimed at evaluating the long-term safety and clinical efficacy (including comparative studies with other urate-lowering agents in hyperuricemic patients with or without gout) are warranted.

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**CONFLICT OF INTEREST**

TH has received consultant fees and/or speakers’ honoraria from Fuji Yakuhin Co., Ltd. and/or Sanwa Kagaku Kenyusho Co., Ltd., the manufacturer of topiroxostat. TS and TO were employees of Fuji Yakuhin Co., Ltd. at the time of the study. HH and RS were employees of Sanwa Kagaku Kenyusho Co., Ltd. at the time of the study.

**SUPPORTING INFORMATION**

Additional Supporting Information may be found in the online version of this article:

Table S1 Methods for each clinical test item.
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