Report on the Deliberation Results

May 8, 2013

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	(a) Topiloric Tablets 20 mg, 40 mg, and 60 mg
	(b) Uriadec Tablets 20 mg, 40 mg, and 60 mg
[Non-proprietary name]	Topiroxostat (JAN*)
[Applicant]	(a) Fujiyakuhin Co., Ltd.
	(b) Sanwa Kagaku Kenkyusho Co., Ltd.
[Date of application]	June 26, 2012

[Results of deliberation]
In the meeting held on April 26, 2013, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product, the re-examination period is 8 years, and neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug.

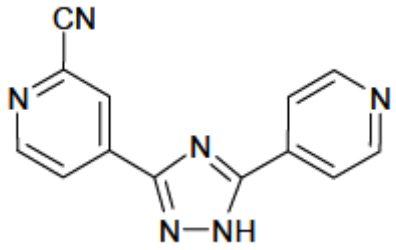
**Japanese Accepted Name (modified INN)*

Review Report

April 15, 2013
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	(a) Topiloric Tablets 20 mg, 40 mg, and 60 mg (b) Uriadec Tablets 20 mg, 40 mg, and 60 mg
[Non-proprietary name]	Topiroxostat
[Applicant]	(a) Fujiyakuhin Co., Ltd. (b) Sanwa Kagaku Kenkyusho Co., Ltd.
[Date of application]	June 26, 2012
[Dosage form/Strength]	Each tablet contains 20, 40, or 60 mg of topiroxostat.
[Application classification]	Prescription drug (1) Drug with a new active ingredient
[Chemical structure]	



Molecular formula: $C_{13}H_8N_6$

Molecular weight: 248.24

Chemical name: 4-[5-(Pyridin-4-yl)-1*H*-1,2,4-triazol-3-yl]pyridine-2-carbonitrile

[Items warranting special mention]	None
[Reviewing office]	Office of New Drug I

Review Results

April 15, 2013

[Brand name]	(a) Topiloric Tablets 20 mg, 40 mg, and 60 mg (b) Uriadec Tablets 20 mg, 40 mg, and 60 mg
[Non-proprietary name]	Topiroxostat
[Applicant]	(a) Fujiyakuhin Co., Ltd. (b) Sanwa Kagaku Kenkyusho Co., Ltd.
[Date of application]	June 26, 2012

[Results of review]

Based on the submitted data, it is concluded that the efficacy of the product in patients with gout or hyperuricaemia has been demonstrated and its safety is acceptable in view of its observed benefits. Safety information on gouty arthritis, hepatic impairment, kidney- or bladder-related adverse events, cutaneous adverse events etc., as well as safety in patients with renal or hepatic impairment and in elderly or female patients needs to be further investigated via post-marketing surveillance.

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the indications and dosage and administration as shown below.

[Indication]	Gout, hyperuricaemia
[Dosage and administration]	The usual adult initial dosage is 20 mg/dose of topiroxostat orally administered twice daily in the morning and evening. Thereafter, the dose should be gradually increased, as needed, while monitoring blood uric acid levels. The usual maintenance dosage should be 60 mg/dose twice daily. The dose may be adjusted according to the patient's condition, up to 80 mg/dose twice daily.

Review Report (1)

March 6, 2013

I. Product Submitted for Registration

[Brand name]	(a) Topiloric Tablets 20 mg, 40 mg, and 60 mg (b) Uriadec Tablets 20 mg, 40 mg, and 60 mg
[Non-proprietary name]	Topiroxostat
[Applicant]	(a) Fujiyakuhin Co., Ltd. (b) Sanwa Kagaku Kenkyusho Co., Ltd.
[Date of application]	June 26, 2012
[Dosage form/Strength]	Each tablet contains 20 mg, 40 mg, or 60 mg of topiroxostat.
[Indication]	Gout, hyperuricaemia
[Dosage and administration]	The usual adult dosage is 20 mg/dose of topiroxostat orally administered twice daily in the morning and evening. Thereafter, the dosage should be gradually increased, as needed, while monitoring blood uric acid levels. The usual maintenance dosage should be 60 mg/dose twice daily. The dose may be adjusted according to the patient's condition, up to 80 mg/dose twice daily.

II. Summary of the Submitted Data and Outline of Review by the Pharmaceuticals and Medical Devices Agency (PMDA)

A summary of the submitted data and an outline of the review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

Topiroxostat, the active ingredient of the six proposed products (hereinafter collectively referred to as "the drug product") including Topiloric Tablets 60 mg and Uriadec Tablets 60 mg, is a xanthine oxidoreductase (XOR) inhibitor developed by Fujiyakuhin Co., Ltd. It is an antihyperuricemic agent that reduces serum uric acid level by selectively inhibiting XOR and thereby suppressing uric acid production.

Antihyperuricemic agents currently used in Japan include uricosuric agents and uric acid production inhibitors. The basic principle is to select uricosuric agents for the uric acid underexcretion type and uric acid production inhibitors for the uric acid overproduction type (Guideline Revision Committee of the Japanese Society of Gout and Nucleic Acid Metabolism, ed. *Guideline for the management of hyperuricaemia and gout: second edition*. 2010). Allopurinol, which, as with topiroxostat, is an XOR inhibitor classified as a uric acid production inhibitor, has been reported to cause serious skin disorders such as toxic epidermal necrolysis and oculomucocutaneous syndrome as clinically significant adverse drug reactions. Moreover, the skin disorders may become serious when accompanied by abnormal

renal function. Administration to patients with renal impairment requires adequate caution and appropriate measures (e.g. dose reduction or discontinuation) because in these patients, delayed excretion of allopurinol and its principal metabolite (oxypurinol) results in prolonged high blood concentrations of these compounds, and in particular, adverse drug reactions in patients with renal impairment may have a serious outcome. Febuxostat was recently approved as a novel XOR inhibitor, and is still in the period to be covered by the re-examination, lacking sufficient clinical experience.

The drug product has been developed as a novel selective XOR inhibitor and is expected to be unaffected by renal condition. The first clinical study of topiroxostat was initiated independently by Fujiyakuhin Co., Ltd. in 20[redacted], and phase III and later development was conducted jointly by Fujiyakuhin Co., Ltd. and Sanwa Kagaku Kenkyusho Co., Ltd. A marketing application has been filed with a claim that the efficacy and safety of topiroxostat in patients with gout or hyperuricaemia have been demonstrated.

Other drugs in the same class (differing in indications for use), which have already been approved in Japan, include uric acid production inhibitors such as allopurinol and febuxostat (approved in December 1968 and January 2011, respectively) and uricosuric agents such as probenecid, bucolome, and benzbromarone (approved in August 1954, December 1966, and August 1978, respectively).

[redacted]

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

[redacted].

2.A.(1).1) Characterization

The drug substance is a white to pale yellow crystalline powder, and its description, solubility, hygroscopicity, thermal analysis, dissociation constants, distribution coefficient, and crystalline polymorphism have been determined. [redacted]. [redacted]. [redacted].

The chemical structure of the drug substance has been elucidated by elementary analysis, mass spectrometry (MS), ultraviolet-visible spectroscopy (UV/Vis), infrared spectrophotometry (IR), nuclear magnetic resonance spectroscopy (^{1}H-, ^{13}C-NMR), and X-ray crystallography.

2.A.(1).2) Manufacturing process

The manufacturing process is shown in the attachment.

2.A.(1).3) Control of drug substance

The proposed specifications for drug substance include content, description, identification (UV/Vis, IR), purity (heavy metals, related substances [liquid chromatography, (HPLC)]), loss on drying, residue on ignition, and assay (potentiometric titration method).

2.A.(1).4) Stability of drug substance

The stability studies of the drug substance are shown in Table 1. Photostability testing demonstrated that the drug substance was photostable.

Table 1. Stability studies of the drug substance

Study	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term	3 production batches	25°C	60% RH	Polyethylene bag + aluminum bag	30 months
Accelerated	3 production batches	40°C	75% RH		6 months

Based on the above, a retest period of 36 months has been proposed for the drug substance when stored at room temperature in a polyethylene bag placed inside an aluminum bag, in accordance with the "Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003, hereinafter referred to as "ICH Q1E Guidelines"). The long-term testing will be continued for up to 36 months.

2.A.(2) Drug product

2.A.(2).1) Description and composition of the drug product, and formulation design

The drug product is an immediate-release uncoated tablet, each containing 20 mg, 40 mg, or 60 mg of topiroxostat. The drug product also contains lactose hydrate, crystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate as excipients.

2.A.(2).2) Manufacturing process

The drug product is manufactured through the process consisting of the following steps: blending, wet granulation, drying, sizing/crushing, granule mixing, and tableting. [redacted].

2.A.(2).3) Control of drug product

The proposed specifications for drug product include content, description, identification, uniformity of dosage units, dissolution, and assay (UV/Vis).

[redacted].

2.A.(2).4) Stability of drug product

The stability studies of the drug product are shown in Table 2. Photostability testing demonstrated that the drug product was photostable.

Table 2. Stability studies of the drug product

Study	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term	3 production batches	25℃	60% RH	PTP sheet or plastic container (only for 40 mg tablets)	24 months
Accelerated	3 production batches	40℃	75% RH		6 months

Based on the above, a shelf life of 36 months has been proposed for the drug product when stored at room temperature in a push-through pack (PTP) (polyethylene film/aluminum foil) or a plastic container (only for 40 mg tablets), in accordance with the ICH Q1E Guidelines. The long-term stability study will be continued for up to 36 months.

2.B Outline of the review by PMDA

Based on the submitted data and the following reviews, PMDA concluded that the quality of the drug substance and the drug product is adequately controlled.

2.B.(1) Control of crystalline polymorphism

PMDA asked the applicant to explain how crystalline polymorphism, which is detected in the drug substance, is controlled.

The applicant responded as follows:

[redacted]. Identification by IR also ensures that the intended crystalline form is produced.

PMDA accepted the applicant’s response.

2.B.(2) Specifications

PMDA asked the applicant to explain whether the drug product specifications are specific enough to identify the drug substance in the drug product.

The applicant responded as follows:

[redacted]. Validation of analytical procedures confirmed that the identification method (HPLC) is specific enough to identify the drug substance in the drug product.

PMDA accepted the applicant's response.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

In primary pharmacodynamic studies, inhibitory activity and mode of inhibition against xanthine oxidoreductase (XOR), inhibitory activity of metabolites against XOR, inhibitory activity against non-XOR enzymes of nucleic acid metabolism were investigated *in vitro*, and the uric acid-lowering effect in hyperuricemic rats etc. were investigated *in vivo*. In safety pharmacology studies, the effects on the central nervous system, cardiovascular system, and respiratory system were investigated. Neither secondary pharmacodynamic study nor pharmacodynamic interaction study was conducted.

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) *In vitro* studies

(a) XOR inhibitory action

i) Enzyme inhibitory action and mode of inhibition (4.2.1.1-1, 4.2.1.1-2)

The actions of topiroxostat, febuxostat, and allopurinol on the production of uric acid from xanthine were studied using XOR purified from bovine milk. The results showed that topiroxostat inhibited XOR in a time-dependent manner. A Lineweaver-Burk plot analysis of the enzymatic reaction demonstrated competitive inhibition when the initial velocity of enzymatic reaction was used. The Ki value of the reaction between topiroxostat and XOR was 5.1 nmol/L when the initial velocity of enzymatic reaction was used, whereas the Ki value of allopurinol was 560 nmol/L. Febuxostat showed mixed inhibition with a Ki (oxidized state) and Ki' (reduced state) of 0.34 nmol/L and 2.0 nmol/L, respectively.

ii) Mechanism of inhibition (4.2.1.1-3, reference data)

The X-ray crystallography of the complex between topiroxostat and XOR purified from bovine milk was performed. The results demonstrated that topiroxostat forms a reaction intermediate through formation of a covalent bond with molybdenum, the reaction center of XOR, via an oxygen atom. It was also shown that topiroxostat interacts with multiple amino acid residues of XOR.

(b) Inhibitory actions of metabolites on XOR (4.2.1.1-4)

The inhibitory actions of major human metabolites of topiroxostat on XOR purified from bovine milk were investigated. The results showed that the IC_{50} values were >100 μmol/L for N_1- and N_2-glucuronide conjugates, 13 μmol/L for topiroxostat N-oxide, and 69 nmol/L for topiroxostat.

(c) Effects on aldehyde oxidase and enzymes of purine and pyrimidine metabolism (4.2.1.1-5, 4.2.1.1-6)

The effects of topiroxostat on aldehyde oxidase, an XOR related enzyme, and on non-XOR enzymes[1] of purine and pyrimidine metabolism were studied. The results showed that topiroxostat (100 μmol/L) inhibited the enzymes tested by only <10%.

(d) Effects on various enzymes and receptor/channel binding capacity (4.2.1.1-7)

The effects of topiroxostat (10, 30, or 100 μmol/L) on activities of 30 types of enzymes and the binding capacity to 54 types of receptors and channels were studied. As a result, topiroxostat (10μmol/L) showed 81% of free radical-scavenging activity (SOD mimetic activity),[2] but it affected no other reactions by ≥50%.

3.(i).A.(1).2) *In vivo* studies

(a) Blood uric acid-lowering effect in rats with potassium oxonate-induced hyperuricaemia (4.2.1.1-8)

Male rats with potassium oxonate-induced[3] hyperuricaemia (n = 5/group) were orally given vehicle,[4] topiroxostat (0.03, 0.1, 0.3, or 1 mg/kg), allopurinol (3, 10, 30, or 100 mg/kg), or febuxostat (1, 3, 10, or 30 mg/kg), and the blood uric acid level was measured over the 24 hours post-dose. The results showed that the blood uric acid level decreased in a dose-dependent manner until 6 hours post-dose in all topiroxostat, allopurinol, and febuxostat groups. At 1 hour post-dose, all treatment groups showed significant decreases in blood uric acid level compared with the control group. At 12 hours post-dose, no significant decrease in blood uric acid level was shown in any allopurinol groups compared with the control group, while the topiroxostat 1 mg/kg and febuxostat 3, 10, and 30 mg/kg groups demonstrated significant decreases in blood uric acid level. At 24 hours post-dose, no significant decrease in the blood uric acid level was shown in any treatment groups compared with the control group.

(b) Blood uric acid-lowering effect in mice with potassium oxonate-induced hyperuricaemia (4.2.1.1-9)

Male mice with potassium oxonate-induced[5] hyperuricaemia (n = 5/group) were orally given vehicle,[4] topiroxostat (0.1, 0.3, or 1 mg/kg), allopurinol (3, 10, or 30 mg/kg), or febuxostat (1, 3, or 10 mg/kg), and the blood uric acid level was measured at 0.5 hour post-dose. The blood uric acid level was also measured at 2 hours after oral administration of vehicle,[4] topiroxostat (0.3, 1, 3 or 10 mg/kg), allopurinol (3, 10, or 30 mg/kg), or febuxostat (1, 3, or 10 mg/kg). The results showed that the blood

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[1] Guanine deaminase, purine nucleoside phosphorylase, hypoxanthine-guanine phosphoribosyltransferase, orotate phosphoribosyltransferase, and orotidine-5'-monophosphate decarboxylase.

[2] Examined by a system in which uric acid and hydrogen peroxide were generated by bovine XOR using xanthine as the substrate. Although this system is used for evaluating SOD mimetic activity against hydrogen peroxide, the applicant considers that topiroxostat showed SOD mimetic activity because inhibition against XOR, the pharmacological activity of topiroxostat, suppressed hydrogen peroxide generation.

[3] Potassium oxonate (250 mg/kg) was administered at 1 hour before and 4, 10, and 22 hours after the test substance dosing.

[4] 0.5% methylcellulose solution

[5] Potassium oxonate (250 mg/kg) was administered at the time of and at 1.5 hours after (0.5 hour before blood collection) the test substance dosing.

uric acid level decreased in a dose-dependent manner in all topiroxostat, allopurinol, and febuxostat groups. All treatment groups showed significant decreases in blood uric acid level compared with the control group at 0.5 hour post-dose. At 2 hours post-dose, all groups except for the topiroxostat 0.3 mg/kg and allopurinol 3 mg/kg showed significant decreases in blood uric acid level compared with the control group.

(c) Blood uric acid-lowering effect and activity to reduce urinary uric acid excretion in chimpanzees loaded with yeast RNA (4.2.1.1-10)

The chimpanzee is an ape that, like humans, lacks uricase, a urate oxidase, and excretes uric acid as the end metabolite of purine. Three male chimpanzees loaded with yeast RNA were orally given 1 mg/kg of topiroxostat after overnight fasting. After a 7- to 8-day recovery period, the chimpanzees were loaded again with yeast RNA, and 5 mg/kg of allopurinol[6] was orally given. The results showed that in comparison with the pre-dose level, the percent decreases in blood uric acid level at 6 and 24 hours post-dose were 30 and 41%, respectively, for topiroxostat, and 19 and 16%, respectively, for allopurinol. In comparison with the level at 24 hours pre-dose, the percent decreases in urinary uric acid excretion (mean ± standard deviation [SD]) during the first and second 24 hours after administration were 24.8% ± 15.8% and 31.7% ± 9.5%, respectively, for topiroxostat and 9.0% ± 4.6% and 4.5% ± 29.2%, respectively, for allopurinol.

3.(i).A.(2) Safety pharmacology studies

3.(i).A.(2).1) Central nervous system (4.2.1.3-1)

Male rats (n = 4/group) were orally given vehicle[4] or topiroxostat (30, 100, or 300 mg/kg), and their behavior and clinical signs were scored and body temperature and locomotor activity were measured. The results showed no changes in behavior, clinical signs, body temperature, or locomotor activity in any treatment groups compared with the control group. Neither death nor signs of toxicity were observed during the 7-day post-dose period. The C_{max} and AUC of topiroxostat at 300 mg/kg, the dose at which no effect was observed, were 892 and 985 times higher, respectively, than those[7] at the maximum recommended clinical dose (160 mg/day).

3.(i).A.(2).2) Cardiovascular system

(a) *In vitro* studies (4.2.1.3-2, 4.2.1.3-3)

The effect of vehicle,[8] topiroxostat (4, 20, or 100 μmol/L), and E-4031[9] (positive control, 0.1 μmol/L) on hERG potassium current was examined in HEK293 cells expressing hERG. The results showed that the hERG current after treatment with 4, 20, and 100 μmol/L of topiroxostat was 89.5% ± 5.8%, 87.6% ± 5.1%, and 83.4% ± 2.0% (mean ± SD), respectively, of pre-treatment values. The

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6 Considering that the clinical maximum dose of allopurinol is 300 mg/day, a calculated dose of 5 mg/kg was set based on a body weight of 60 kg.

7 Calculated based on Study FYX-051-112, which showed that C_{max} was 609 ng/mL and AUC was 2274 ng·h/mL (value of 1137 ng·h/mL [$AUC_{0\text{-}12\,h}$] multiplied by 2) when 80 mg of topiroxostat was orally administered twice daily (160 mg in 2 doses) for 7 days to healthy Japanese adult men.

8 0.1% DMSO solution

9 Dissolved in water for injection.

hERG current after treatment with E-4031 and vehicle was 4.7% ± 2.6% and 88.5% ± 4.1%, respectively, of pre-treatment values. The hERG current was thus reduced by the positive control but unaffected by topiroxostat.

Using papillary muscle isolated from the right ventricle of male guinea pigs, the effect of vehicle,[8] topiroxostat (4, 20, or 100 μmol/L), and sotalol (positive control, 30 μmol/L) on the following action potential parameters was investigated: the resting membrane potential (RMP), action potential amplitude (APA), action potential duration at 50% and 90% repolarization (APD_{50} and APD_{90}), and maximum upstroke velocity (V_{max}). The results showed that topiroxostat had no effect at concentrations up to 20 μmol/L. At 100 μmol/L, topiroxostat shortened APD_{50} and APD_{90} to 58.1% ± 29.3% and 64.7% ± 25.9% (mean ± SD), respectively, of pre-treatment values, and slightly reduced RMP and APA to 97.2% ± 1.6% and 98.1% ± 1.2%, respectively, of pre-treatment values, but did not affect V_{max}. On the other hand, sotalol treatment did not affect RMP, APA, or V_{max}, but prolonged APD_{50} and APD_{90} to 119.9% ± 8.1% and 123.4% ± 8.0% (mean ± SD), respectively, of pre-treatment values.

(b) *In vivo* study (4.2.1.3-4)

Male and female dogs (2 each) were orally given vehicle[4] or topiroxostat (3, 10, or 30 mg/kg) in a crossover fashion, and their blood pressure, heart rate, and lead II electrocardiogram (ECG) were monitored during the 12-hour post-dose period. The results showed a slight increase in heart rate between 0 and 2 hours post-dose in the 30 mg/kg group (mean value, 75/min in the control group vs. 88/min in the 30 mg/kg group), but this change did not persist. No effect was observed on blood pressure or lead II ECG.

3.(i).A.(2).3) Respiratory system (4.2.1.3-5)

Male rats (n = 8/group) were orally given vehicle[4] or topiroxostat (30, 100, or 300 mg/kg), and the effect on respiratory function was investigated by whole body plethysmography. The results showed an increase in minute respiratory volume only at 150 minutes after administration of 300 mg/kg of topiroxostat, but this increase was considered to be due to a low level of minute respiratory volume in the control group at the corresponding time point, and therefore incidental. Thus, administration of topiroxostat did not affect respiration rate and tidal volume.

3.(i).B Outline of the review by PMDA

3.(i).B.(1) Differences in the mode of XOR inhibition between topiroxostat and other agents in the same class

PMDA asked the applicant to explain the differences in the mode of inhibition against XOR between topiroxostat and other agents in the same class (allopurinol and febuxostat) and how these differences were reflected in the pharmacological effects of topiroxostat.

The applicant responded as follows:

Molybdenum, the active center of XOR, changes its redox state by the progression of catalysis, with a valence of 4 or 6. When a substrate, such as hypoxanthine or xanthine, is hydroxylated by XOR, molybdenum (Mo) is reduced from hexavalent, Mo(VI), to tetravalent, Mo(IV). Subsequently Mo(IV) is reoxidized to Mo(VI) when the generated xanthine and uric acid dissociate from the enzyme.

Allopurinol, as with hypoxanthine and xanthine, is a substrate of XOR, and is hydroxylated to oxypurinol by XOR. Accumulated oxypurinol forms a strong covalent bond with Mo(IV), and exerts inhibitory activity against XOR (Massey V, *et al*., *J Biol Chem*. 1970;245:2837-44). Allopurinol has little interaction with the amino acid residues in the substrate pocket of XOR, and shows only weak competitive inhibition with a Ki value of 560 nmol/L against Mo(VI). Therefore, when Mo(IV) is reoxidized to Mo(VI), oxypurinol dissociates from XOR with a dissociation half-time ($t_{1/2}$) of 5 hours, resulting in a rapid loss of inhibitory activity.

Febuxostat forms no covalent bond with molybdenum, and binds strongly with XOR by filling the space in the substrate pocket in addition to exhibiting interactions with amino acid residues. It has therefore been reported that the effect of febuxostat is not dependent on the redox state of molybdenum, and significantly inhibits XOR in both Mo(IV) and Mo(VI) states, thus showing mixed inhibition against XOR (Ki and Ki' at steady state are 0.12 nmol/L and 0.9 nmol/L, respectively) (Okamoto K, *et al*., *J Biol Chem*. 2003;278:1848-55).

Topiroxostat, like allopurinol, is a substrate of XOR and is hydroxylated by XOR. However, unlike allopurinol, X-ray crystallography has shown that topiroxostat forms a covalent bond with Mo(IV) via an oxygen atom at a position ortho to the nitrogen atom of the pyridine ring bound to the 5-position of the triazole ring, and forms a stable reaction intermediate. In addition, both topiroxostat and febuxostat form hydrogen bonds with multiple amino acid residues of XOR (between the cyano group of topiroxostat and Asn768; between the unsubstituted pyridine ring nitrogen of topiroxostat and Glu1261; between the triazole ring nitrogen of topiroxostat and Glu802) and through interactions between aromatic rings (interactions of the triazole ring of topiroxostat with Phe914 and Phe1009 of XOR) (Okamoto K, *et al*., *Proc Natl Acad Sci USA*. 2004;101:7931-6). Therefore, topiroxostat is considered to inhibit XOR through the formation of not only a covalent bond but also through interactions such as the formation of hydrogen bonds. Studies on the activity and mode of enzyme inhibition (4.2.1.1-1 and 4.2.1.1-2) determined Ki values of 5.1 nmol/L and 560 nmol/L for inhibition by topiroxostat and allopurinol, respectively, of XOR with molybdenum being hexavalent. Examination of the persistence of the inhibitory effect on XOR revealed that oxypurinol, a metabolite of allopurinol, bound exclusively to Mo(IV) and dissociated from XOR with a dissociation half-time ($t_{1/2}$) of 5 hours when Mo(IV) was reoxidized to Mo(VI). On the other hand, topiroxostat dissociated slowly from the enzyme with a $t_{1/2}$ of 20.4 hours since the interactions of topiroxostat include not only the covalent bond with Mo(IV) but also the hydrogen bonds with Mo(VI) (Matsumoto K, *et al*., *J Pharmacol Exp Ther*. 2011;336:95-103).

The above findings show that topiroxostat has a combined mode of XOR inhibition of allopurinol and febuxostat. Topiroxostat not only forms a covalent bond but also participates in other interactions with XOR, including hydrogen bonds, and thereby exhibits uric acid-lowering effect *in vivo* by binding to XOR in both Mo(IV) and Mo(VI) states.

PMDA accepted the applicant's response.

3.(i).B.(2) Pharmacodynamic effects of repeated administration of topiroxostat

PMDA asked the applicant to explain the effects of repeated administration of topiroxostat on its blood uric acid-lowering effect and formation of xanthine calculi.

The applicant responded as follows:

Although the blood uric acid-lowering effect by repeated administration has not been investigated in animal models, blood xanthine concentration was evaluated in a 4-week repeated oral dose toxicity study in rats (4.2.3.2-1). When measured after a single dose or 4-week repeated oral doses of 1 or 3 mg/kg of topiroxostat, blood xanthine concentrations increased in a dose-dependent manner after a single dose with the maximum concentration being reached at 4 or 8 hours post-dose, and a similar time course was observed after 4-week repeated oral doses. The possibility of topiroxostat-induced xanthine calculus formation was investigated in a 13-week repeated oral dose toxicity study in rats (4.2.3.2-2), in which yellowish white granular material was detected in the kidney and bladder and was identified as xanthine calculi from the results of high-speed liquid chromatography/tandem mass spectroscopy (LC-MS/MS). In the repeated oral dose toxicity study of topiroxostat in rats, the yellowish white granular material was not detected in the kidney after 4 weeks of administration (0.3, 1, or 3 mg/kg) but was detected at doses of ≥1 mg/kg after 13-week administration at 0.3, 1, or 3 mg/kg and at doses of ≥0.2 mg/kg after 26-week administration at 0.04, 0.2, or 1 mg/kg. In the repeated oral dose toxicity study of topiroxostat in dogs, the yellowish white granular material was not detected in the kidney after 4 weeks of administration (3, 10, or 30 mg/kg) but was detected at 100 mg/kg after 13 weeks of administration at 10, 30, or 100 mg/kg. In the repeated oral dose toxicity study of topiroxostat in monkeys, the yellowish white granular material was not detected in the kidney after 13 weeks of administration at 10, 30, or 100 mg/kg and 52 weeks of administration at 30, 100, or 300 mg/kg. The results showed that repeated oral doses of topiroxostat induced formation of xanthine calculi in rats and dogs, suggesting that the prolonged period of topiroxostat administration enhanced xanthine calculus formation in rats. The applicant considered that the above species differences in formation of xanthine calculi involve factors including the amount of urinary purine metabolites, exposure to topiroxostat, and urine solubility of xanthine, and that in rats, the combined action of these factors resulted in formation of xanthine calculi at low topiroxostat doses. Given that the amount of urinary purine metabolites, a major factor for the species differences in the formation of xanthine calculi, was similar between humans and monkeys, and that xanthine calculi were not formed in monkeys, topiroxostat administration is unlikely to induce formation of xanthine calculi in humans. In a phase I multiple dose study (Study FYX-051-112), no xanthine crystal was detected in the sediment

of casual urine samples during 7-day twice-daily administration of topiroxostat at up to 80 mg/dose. A pooled analysis of double-blind studies in human patients (pooled double-blind study analysis)[10] showed that the incidence of the adverse drug reaction "ureteral calculus" was 0.0% (0 of 135 subjects) in the placebo group and 0.2% (1 of 465 subjects) in the topiroxostat group.

The above findings suggest that the blood uric acid-lowering effect after the first dose of topiroxostat is maintained at similar levels after repeated doses. The formation of xanthine calculi is enhanced in rats, but is unlikely to occur in humans.

Although PMDA accepted the above response in terms of non-clinical findings, PMDA will further discuss formation of xanthine calculi and the effect on the kidney in the toxicological and clinical sections [see "3.(iii).B.(1) Nephrotoxicity" and "4.(iii).B.(3).3) Kidney or bladder-related adverse events"].

3.(i).B.(3) Effect on cardiovascular system

Since APD was shortened during treatment with topiroxostat in an *in vitro* study using guinea pig papillary muscle (4.2.1.3-3), and heart rate increased in a study on the cardiovascular effects in dogs (4.2.1.3-4), PMDA requested the applicant to explain the mechanisms of these events and safety in humans.

The applicant responded as follows:

Given that the concentration at which the shortening of APD_{50} and APD_{90} was observed (100 μmol/L) was approximately 710-fold higher than the maximum free-drug concentration in plasma[11] (0.14 μmol/L) after topiroxostat administration at the recommended clinical dose, the APD shortening effect by topiroxostat is unlikely to occur in humans. Note that the APD shortening effect is known to be caused by lidocaine and mexiletine, which are sodium channel blockers classified as Class Ib by the Vaughan Williams classification of antiarrhythmic drugs (Bigger JT, *et al.*, Goodman and Gilman's The Pharmacological Basis of Therapeutics, 8th ed., Tokyo, Hirokawa Shoten Co., 1992;1045-51). Various ion channels including sodium channels were not affected by 100 μmol/L of topiroxostat in a study on the binding capacity to ion channels (4.2.1.1-7), and the APD shortening effect observed in the *in vitro* study using guinea pig papillary muscle was therefore possibly due to a nonspecific effect. APD shortening raises concerns about cardiac effects such as shortening of ECG waves or an increase in heart rate. Of non-clinical studies on topiroxostat, a study on the cardiovascular effects in dogs (4.2.1.3-4) showed a transient increase in heart rate after administration of 30 mg/kg of topiroxostat, but no abnormality was observed on ECG. No abnormalities of heart rate or ECG were detected after administration of topiroxostat at 100 mg/kg in a 13-week repeated oral dose toxicity study in dogs

[10] Pooled analysis of Studies FYX-051-221, FYX-051-222, FYX-051-323, FY1001, and FY1003

[11] The applicant calculated the value, assuming a middle dose of 120 mg/day and a maximum dose of 160 mg/day as the recommended clinical doses of topiroxostat. Given that the higher C_{max} value of those obtained in the two clinical studies for a single dose of 80 mg of topiroxostat (Studies FYX-051-124 and FYX-051-135) was 1794.9 ng/mL, and that the binding rate of topiroxostat to human plasma proteins is approximately 98% (Study F0684), the concentration of free unchanged topiroxostat was estimated to be 35.9 ng/mL (1794.9 ng/mL × [100 – 98]/100) following a dose of 80 mg, the maximum recommended clinical dose of topiroxostat, and this concentration was converted to a molar concentration of 0.14 μmol/L (molecular weight, 248.24).

(4.2.3.2-5) and at 300 mg/kg in a 52-week repeated oral dose toxicity study in monkeys (4.2.3.2-7). The results of heart rate measured every 10 minutes for 2 hours after administration showed that in the 30 mg/kg group, heart rate increased only at 1 hour 10 minutes post-dose without any previous or subsequent increase, and otherwise showed no difference from the control group. Therefore, this increase in heart rate was considered to be incidental and not to be due to the pharmacological effect of topiroxostat. Note that the exposure parameters, C_{max} and AUC, of topiroxostat were 12 and 15 times higher, respectively, at 30 mg/kg than at the maximum recommended clinical dose (160 mg/day). Also in a clinical study in humans, QT/QTc interval was not affected in a QT/QTc evaluation study of a single 60 or 180 mg dose of topiroxostat.

Based on the above, although the detailed mechanism of APD shortening is unknown, clinical use of topiroxostat is unlikely to raise concerns about the APD shortening effect because: parameters including hERG channel were unaffected in *in vitro* studies; no influence of APD shortening was observed in non-clinical or clinical studies; and the concentration at which APD was shortened greatly differed from the plasma topiroxostat concentration at the maximum recommended clinical dose.

PMDA accepted the applicant's response.

3.(ii) Summary of pharmacokinetic studies

3.(ii).A Summary of the submitted data

The pharmacokinetics of topiroxostat and ^{14}C-topiroxostat was analyzed after a single oral or intravenous dose to rats, dogs, and monkeys and after repeated oral doses to rats. The plasma concentrations of unchanged topiroxostat and topiroxostat N-oxide in each animal species were measured by LC-MS/MS, with the lower limit of quantification being 1 ng/mL for both analytes. The plasma concentrations of N_1- and N_2-glucuronide conjugates of topiroxostat in monkeys were measured by HPLC with UV detector (HPLC-UV), with the lower limit of quantification being 0.1 μg eq./mL. Radioactivity in biological samples was measured by liquid scintillation counting (LSC), liquid chromatography/mass spectroscopy (LC-MS), HPLC with radioactivity detector (HPLC-RAD), or autoradiography.

3.(ii).A.(1) Absorption (4.2.2.2-1 to 2, 4.2.2.2-4 to 7)

Table 3 shows the pharmacokinetic parameters of unchanged topiroxostat in the plasma of male and female rats (n = 5/group), male dogs (n = 4/group), and male monkeys (n = 3/group) after a single oral or intravenous dose of topiroxostat under fasting conditions.

Table 3. Pharmacokinetic parameters of unchanged topiroxostat in plasma after a single oral or intravenous dose under fasting conditions

Animal species	Route of adminis-tration	Dose (mg/kg)	Sex (n)	C_0 or C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\text{-inf}}$ (ng·h/mL)	$T_{1/2}$ (h)	CL_{tot} (L/h/kg)	BA[a)] (%)
Rat	p.o.	0.3	Male (5)	276.8 ± 92.8	0.30 ± 0.11	404.8 ± 61.6	4.79 ± 1.65	–	–
		1	Male (5)	1116.0 ± 174.4	0.35 ± 0.14	3366.0 ± 1274.0	4.83 ± 1.02	–	69.6
			Female (5)	1708.5 ± 139.5	0.25 ± 0.00	4160.0 ± 636.2	4.67 ± 1.97	–	66.9
		3	Male (5)	5432.6 ± 684.8	0.35 ± 0.14	22398.4 ± 2201.0	5.92 ± 1.37	–	–
	i.v.	1	Male (5)	2880.1 ± 421.8	–	4838.8 ± 669.0	5.18 ± 1.54	0.21 ± 0.03	–
			Female (5)	2987.4 ± 235.8	–	6219.9 ± 655.1	5.13 ± 2.87	0.16 ± 0.02	–
Dog	p.o.	0.3	Male (4)	88.8 ± 23.8	0.44 ± 0.13	NC	NC	–	–
		1	Male (4)	382.3 ± 84.7	0.94 ± 0.77	684.2 ± 93.3	5.75 ± 4.10	–	59.6
		3	Male (4)	1177.5 ± 206.7	0.88 ± 0.25	2734.2 ± 419.0	5.02 ± 1.81	–	–
	i.v	1	Male (4)	1095.5 ± 101.9	–	1148.5 ± 286.7	3.51 ± 2.39	0.92 ± 0.23	–
Monkey	p.o.	1	Male (3)	219.0 ± 150.4	1.00 ± 0.87	517.2 ± 213.7	4.23 ± 0.56	–	79.6
	i.v.		Male (3)	1404.2 ± 489.9	–	649.4 ± 155.0	4.06 ± 1.38	1.59 ± 0.35	–

Mean ± SD; –, not applicable; NC, not calculated

C_0, initial plasma concentration extrapolated to time = 0 when administered intravenously; C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration; $AUC_{0\text{-inf}}$, area under the plasma concentration-time curve extrapolated to t = infinity; $T_{1/2}$, elimination half-life; CL_{tot}, total body clearance; BA, bioavailability

a) Mean

Table 4 shows the pharmacokinetic parameters for plasma radioactivity levels in male rats (n = 3) to which once-daily oral repeated doses of ^{14}C-topiroxostat were given for 14 days under fed conditions.

Table 4. Pharmacokinetic parameters of plasma radioactivity during repeated once-daily oral administration of ^{14}C-topiroxostat for 14 days under fed conditions

Dose (mg/kg)	Sex (n)	Day of measurement	C_{max} (ng eq./mL)	T_{max} (h)	$AUC_{0\text{-24 h}}$ (ng eq.·h/mL)	$T_{1/2}$[a)] (h)	CL_{tot}/F (mL/h/kg)
0.3	Male (3)	Day 1	69.0 ± 1.8	0.8 ± 0.3	454.6 ± 33.6	11.0 ± 1.3	537.9 ± 26.0
		Day 7	92.5 ± 19.5	1.0 ± 0.0	639.7 ± 49.6	13.1 ± 4.0	352.1 ± 38.3
		Day 14	115.6 ± 18.0	1.3 ± 0.6	843.2 ± 156.8	11.7 ± 2.6	219.3 ± 50.7

Mean ± SD

C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration; $AUC_{0\text{-24 h}}$, area under the plasma concentration-time curve until 24 hours post-dose; $T_{1/2}$, elimination half-life; CL_{tot}/F, apparent total body clearance

a) Calculated from 4 to 24 hours post-dose

The pharmacokinetic parameters of plasma radioactivity on Day 7 and Day 14 relative to Day 1 showed 1.3- and 1.7-fold increase, respectively, for C_{max} and 1.4- and 1.9-fold increase, respectively, for $AUC_{0\text{-24 h}}$.

Table 5 shows the pharmacokinetic parameters of radioactivity in the plasma of male rats (n = 3/group) after administration of a single oral dose of ^{14}C-topiroxostat under fasting or fed conditions. Table 6 shows the pharmacokinetic parameters of unchanged topiroxostat in the plasma of male dogs (n = 4/group) after administration of a single oral dose of topiroxostat under fasting or fed conditions.

Table 5. Pharmacokinetic parameters of plasma radioactivity after administration of a single oral dose of ^{14}C-topiroxostat under fasting or fed conditions

Animal species	Dose (mg/kg)	Sex (n)	Dosing conditions	C_{max} (ng eq./mL)	T_{max} (h)	$AUC_{0\text{-inf}}$ (ng eq.·h/mL)	$T_{1/2}$ [a)] (h)	CL_{tot}/F (mL/h/kg)
Rat	1	Male (3)	Fasting	1432.4 ± 87.5	0.42 ± 0.14	6344 ± 1712	19.7 ± 1.1	164.7 ± 39.4
		Male (3)	Fed	351.5 ± 41.5	1.67 ± 0.58	3722 ± 175	23.5 ± 5.8	269.1 ± 12.6

Mean ± SD

C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration; $AUC_{0\text{-inf}}$, area under the plasma concentration-time curve extrapolated to t = infinity; $T_{1/2}$, elimination half-life; CL_{tot}/F, apparent total body clearance

a) Calculated from 12 to 72 hours post-dose

Table 6. Pharmacokinetic parameters of unchanged topiroxostat in plasma after administration of a single oral dose of topiroxostat under fasting or fed conditions

Animal species	Dose (mg/kg)	Sex (n)	Dosing conditions	C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\text{-}inf}$ (ng·h/mL)	$T_{1/2}$ (h)	CL_{tot}/F (mL/h/kg)
Dog	1	Male (4)	Fasting	382.3 ± 84.7	0.94 ± 0.77	684.2 ± 93.3	5.75 ± 4.10	NC
		Male (4)	Fed	170.8 ± 55.7	2.00 ± 0.82	797.4 ± 105.9	4.91 ± 4.21	NC

Mean ± SD; NC, not calculated

C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration; $AUC_{0\text{-}inf}$, area under the plasma concentration-time curve extrapolated to t = infinity; $T_{1/2}$, elimination half-life; CL_{tot}/F, apparent total body clearance

A single dose of 0.6 mg of ^{14}C-topiroxostat was injected into the ligated gastrointestinal loops of male rats (n = 3) under fasting conditions. The absorption in each gastrointestinal portion during the 1 hour after injection (mean ± SD, percentage of the injected radioactivity) was 23.5% ± 6.2% in the stomach, 47.5% ± 2.4% in the duodenum, 60.1% ± 1.7% in the jejunum, 45.0% ± 5.9% in the ileum, and 25.0% ± 6.0% in the colon.

3.(ii).A.(2) Distribution (4.2.2.3-1 to 4, 4.2.2.3-6 to 7)

Tissue radioactivity level was measured in male and female rats (n = 3/sex//time point) after administration of a single oral dose of 1 mg/kg of ^{14}C-topiroxostat under fasting conditions. In male rats, the highest radioactivity level was reached at 2 hours post-dose in the small intestine, bladder, and testis, at 6 hours post-dose in the large intestine, at 24 hours post-dose in the skin, and at 30 minutes post-dose in other tissues. At 24 hours post-dose, the radioactivity levels in tissues other than the skin were ≤14.9% of the highest radioactivity level or below the lower limit of quantification. The tissues showing high radioactivity levels at 24 hours post-dose included the skin and kidney, in which radioactivity levels were 88.9 and 70.6 times, respectively, the plasma radioactivity level. The radioactivity levels in other tissues were ≤11.5 times the plasma radioactivity level or below the lower limit of quantification. At 72 hours post-dose, the radioactivity level was 44.2% of the highest radioactivity level in the skin, but was ≤2.2% of the highest radioactivity level or below the lower limit of quantification in other tissues. At 168 hours post-dose, the radioactivity level was ≤0.8% of the highest radioactivity level or below the lower limit of quantification in all tissues. In female rats, the highest radioactivity level was reached at 6 hours post-dose in the large intestine and at 30 minutes post-dose in other tissues. At 24 hours post-dose, the radioactivity level was ≤9.2% of the highest radioactivity level or below the lower limit of quantification in all tissues. The tissue showing high radioactivity level at 24 hours post-dose was the kidney, in which radioactivity level was 31.2 times the plasma radioactivity level. The radioactivity levels in other tissues were ≤7.2 times the plasma radioactivity level or below the lower limit of quantification.

Tissue radioactivity level was measured in male pigmented rats (n = 3/time point) after administration of a single oral dose of 1 mg/kg of ^{14}C-topiroxostat under fasting conditions. The results showed that the highest radioactivity level was reached at 2 hours post-dose in the eye and at 30 minutes post-dose in other tissues. The tissues showing high radioactivity levels at 24 hours post-dose included the kidney, white skin, eye, liver, and pigmented skin, in which the radioactivity levels were 43.8, 20.4, 18.7, 9.5, and 5.7 times, respectively, the plasma radioactivity level. At 336 hours post-dose, the radioactivity levels in all tissues were ≤4% of the highest radioactivity level. The elimination half-life

of radioactivity in the eye after the 6-hour post-dose period was 69 hours, and those in the pigmented skin, blood, white skin, liver, and kidney after the 2-hour post-dose period were 101, 53, 48, 44, and 38 hours, respectively.

Tissue radioactivity level was measured in male rats (n = 3/time point) following repeated oral doses of 0.3 mg/kg of ^{14}C-topiroxostat once daily for 14 days. The tissue radioactivity level at 24 hours post-dose showed a tendency to increase with the number of doses, and the radioactivity level at 14 days post-dose was 0.9 to 5.4 times that on the first day of administration. Tissue distribution at 14 days post-dose showed high radioactivity levels in the liver, skeletal muscle, and skin, which decreased with the decrease in plasma radioactivity level.

Tissue radioactivity level was measured in pregnant rats (gestation day 19, n = 3/time point) after administration of a single oral dose of 1 mg/kg ^{14}C-topiroxostat under fasting conditions. Fetal radioactivity level reached the highest level of 308.7 ng eq./g (0.25 times the maternal plasma radioactivity level) at 30 minutes post-dose, but decreased to 42% and 8% of the highest level at 6 and 24 hours post-dose, respectively.

Mean protein binding (ultrafiltration method) of ^{14}C-topiroxostat (20-2000 ng/mL) in the plasma of rats, dogs, and monkeys was 97.5% to 98.7%, 96.7% to 97.9%, and 97.5% to 99.3%, respectively.

Mean distribution of ^{14}C-topiroxostat (20-2000 ng/mL) in blood cells in rats, dogs, and monkeys was 0.0% to 1.1%, 46.0% to 51.1%, and 19.3% to 27.1%, respectively [for human data, see "4.(ii).A.(1) Studies using human biomaterials"].

3.(ii).A.(3) Metabolism (4.2.2.4-2 to 7)

Male rats (n = 3/time point) received a single oral dose of 1 mg/kg of ^{14}C-topiroxostat under fasting conditions. As a result, the mean percentages of radioactivity in plasma at 30 minutes, 2 hours, and 6 hours post-dose were 93.2%, 89.8%, and 67.6%, respectively, for unchanged topiroxostat, 1.2%, 1.1%, and 1.0%, respectively, for topiroxostat N-oxide, and 0.4%, 0.6%, and 1.7%, respectively, for 2-hydroxy-topiroxostat. The mean percentage of radioactivity in urine collected up to 24hours post-dose was 0.8% for unchanged topiroxostat, 46.5% for topiroxostat N-oxide, 11.3% for 2-hydroxy-topiroxostat, 2.9% for N_1-glucuronide conjugate, 2.7% for N_2-glucuronide conjugate, and 1.7% for N_1-glucose conjugate.

Bile duct-cannulated male rats (n = 3/time point) received a single oral dose of 1 mg/kg of ^{14}C-topiroxostat under fasting conditions. As a result, the mean percentage of radioactivity in bile collected up to 12 hours post-dose was 3.5% for unchanged topiroxostat, 63.5% for topiroxostat N-oxide, 4.3% for 2-hydroxy-topiroxostat, 1.9% for N_1-glucuronide conjugate, 1.2% for N_2-glucuronide conjugate, and 1.0% for N_1-glucose conjugate.

Male rats (n = 3/time point) received a single oral dose of 1 mg/kg of ^{14}C-topiroxostat under fasting conditions. As a result, the percentages of radioactivity at 2, 6, and 24 hours post-dose (calculated from the combined tissues of 3 animals) were: in the liver, 61.6%, 55.9%, and 10.4%, respectively, for unchanged topiroxostat, 2.1%, 3.6%, and 0.0% (below the limit of quantification), respectively, for topiroxostat N-oxide, and 4.1%, 8.5%, and 40.6%, respectively, for 2-hydroxyl-topiroxostat; in the kidney, 47.0%, 29.4%, and 1.3%, respectively, for unchanged topiroxostat, 4.8%, 23.3%, and 27.3%, respectively, for topiroxostat N-oxide, and 1.6%, 7.3%, and 19.3%, respectively, for 2-hydroxy-topiroxostat; and in the skin, 37.2%, 12.9%, and 0.0% (below the limit of quantification), respectively, for unchanged topiroxostat and 15.2%, 24.4%, and 13.1%, respectively, for 2-hydroxy-topiroxostat.

Male and female rats (n = 3/sex/time point) received a single oral dose of 1 mg/kg of ^{14}C-topiroxostat under fasting conditions. As a result, the mean percentages of radioactivity in urine collected during the 24 hours post-dose (calculated from the combined urine of 3 animals) was, in males and females, 1.4% and 1.1%, respectively, for unchanged topiroxostat, 50.5% and 51.7%, respectively, for topiroxostat N-oxide, 11.6% and 20.4%, respectively, for 2-hydroxy-topiroxostat, 3.5% and 1.8%, respectively, for N_1-glucuronide conjugate, and 2.3% and 1.6%, respectively, for N_2-glucuronide conjugate. The percentage of radioactivity in feces collected up to 24 hours post-dose (calculated from the combined feces of 3 animals) in males and females was 29.6% and 18.5%, respectively, for unchanged topiroxostat and 18.7% and 28.6%, respectively, for 2-hydroxy-topiroxostat.

Male dogs (n = 3/time point) received a single oral dose of 1 mg/kg of ^{14}C-topiroxostat under fasting conditions. As a result, the mean percentages of radioactivity in plasma at 30 minutes, 2 hours, and 6 hours post-dose were 56.6%, 41.3%, and 8.3%, respectively, for unchanged topiroxostat, 1.1%, 2.9%, and 4.1%, respectively, for N_1-glucuronide conjugate, 11.7%, 23.4%, and 24.3%, respectively, for N_1-glucose conjugate, and 5.4%, 8.8%, and 9.5%, respectively, for N_2-glucose conjugate. The mean percentage of radioactivity in urine collected during the 24 hours post-dose was 0.6% for unchanged topiroxostat, 12.0% for topiroxostat N-oxide, 1.1% for 2-hydroxy-topiroxostat, 5.7% for N_1-glucuronide conjugate, 1.8% for N_2-glucuronide conjugate, 37.4% for N_1-glucose conjugate, and 16.3% for N_2-glucose conjugate.

Male monkeys (n = 3) received a single oral dose of 1 mg/kg of topiroxostat under fasting conditions. As a result, $AUC_{0\text{-inf}}$ of unchanged topiroxostat and glucuronide conjugates (total of N_1- and N_2-glucuronide conjugates) was 517.2 and 963.9 ng eq.·h/mL, respectively. topiroxostat N-oxide was detected in a trace amount, but $AUC_{0\text{-inf}}$ was not calculated. In urine collected up to 48 hours post-dose, the mean percentage of the administered radioactivity was 0.4% for unchanged topiroxostat, 0.1% for topiroxostat N-oxide, and 49.4% for glucuronide conjugates.

N_1- and N_2-glucuronide conjugates and topiroxostat N-oxide in plasma were quantitated in the samples remaining after the 52-week repeated dose toxicity study in monkeys (4.2.3.2-7). C_{max} and $AUC_{0\text{-}24\ h}$

showed a slight tendency to increase over the periods from the day of the first dose to Weeks 25 and 52.

3.(ii).A.(4) Excretion (4.2.2.2-3, 4.2.2.5-1 to 2)

Male and female rats (n = 3/sex/time point) received a single oral dose of 1 mg/kg of ^{14}C-topiroxostat under fasting conditions. As a result, cumulative urinary excretion (mean percentage of the administered radioactivity) was 34.7% in males and 48.2% in females, and cumulative fecal excretion was 60.1% in males and 46.5% in females, both during the 168 hours post-dose.

Bile duct-cannulated male rats (n = 3/time point) received a single oral dose of 1 mg/kg of ^{14}C-topiroxostat under fasting conditions. As a result, cumulative excretion of radioactivity (mean percentage of the administered radioactivity) into bile, urine, and feces up to 48 hours post-dose was 73.0%, 14.7%, and 5.5%, respectively.

A single oral dose of 1 mg/kg of ^{14}C-topiroxostat was administered to bile duct-cannulated male rats (n = 3/time point) under fasting conditions, and bile was collected up to 12 hours post-dose. An aliquot of the obtained bile sample (containing 11.1 μg/mL/body as topiroxostat) was injected into the duodenum of other bile duct-cannulated male rats, in which 43.1%, 11.1%, and 40.8% of radioactivity (mean percentage of the injected radioactivity) were excreted into bile, urine, and feces, respectively, up to 48 hours after the injection.

Male and female dogs (n = 3/sex/time point) received a single oral dose of 1 mg/kg of ^{14}C-topiroxostat under fasting conditions. As a result, cumulative urinary excretion of radioactivity (mean percentage of the administered radioactivity) was 20.3% in males and 22.4% in females, and cumulative fecal excretion was 77.4% in males and 77.0% in females, both up to 168 hours post-dose.

Lactating rats (lactation days 8-10, n = 3/time point) received a single oral dose of 1 mg/kg of ^{14}C-topiroxostat under fed conditions. As a result, the radioactivity in milk reached C_{max} (3594.8 ng eq./mL) at 3.3 hours post-dose with a $T_{1/2}$ of 10.4 hours and an $AUC_{0\text{-inf}}$ of 64,730 ng eq.·h/mL. Simultaneously, the radioactivity in plasma was measured, and it reached C_{max} (555.6 ng eq./mL) at 1.0 hour post-dose with a $T_{1/2}$ of 4.7 hours and an $AUC_{0\text{-inf}}$ of 4293 ng eq.·h/mL.

3.(ii).A.(5) Drug interactions (4.2.2.6-1)

The effects on liver enzymes involved in drug metabolism were investigated in female rats (n = 5/group) which repeatedly received either once-daily oral doses of vehicle,[4] 1, 3, or 10 mg/kg of topiroxostat for 7 days, or intraperitoneal doses of 80 mg/kg phenobarbital sodium (positive control) for 3 days. The results showed no difference between the topiroxostat groups at all doses and the control group in terms of body weight, relative liver weight, microsomal protein content, cytochrome P450 content, cytochrome b5 content, NADPH-cytochrome c reductase activity, aniline p-hydroxylation activity, 7-ethoxycoumarin O-deethylation activity, and aminopyrine n-demethylation

activity.

3.(ii).B Outline of the review by PMDA

3.(ii).B.(1) Distribution to skin

PMDA asked the applicant to explain the reason why, in the rat distribution study (4.2.2.3-1), radioactivity in male rats showed higher concentrations in the skin than in the plasma, and remained in the skin at 72 hours post-dose, and to discuss the possibility of persistent topiroxostat residues in human skin.

The applicant responded as follows:

In the rat distribution study (4.2.2.3-1), the skin radioactivity level in male rats increased over time up to 24 hours post-dose, and reached its peak (mean, 1155.0 ng eq./g) at 24 hours post-dose. The radioactivity level at 24 hours post-dose was 89 times higher in the skin than in the plasma (13.0 ng eq./mL). Thereafter, the skin radioactivity level decreased over time to 510.7 and 7.3 ng eq./g at 72 and 168 hours post-dose, respectively. On the other hand, the plasma radioactivity level reached its peak (1497.9 ng eq./mL) at 30 minutes post-dose, followed by a decrease over time. The study of metabolites in male rat tissues (4.2.2.4-3) showed that the recovery of radioactivity from skin tissue was 80.1% at 2 hours post-dose, but decreased to 50.2% and 24.5% at 6 and 24 hours post-dose, respectively. The skin radioactivity levels at 2, 6, and 24 hours post-dose were 386.0, 215.7, and 290.4 ng eq./g, respectively, with no major difference. Therefore, the decrease in the recovery of radioactivity in the skin is considered to be due to a time-dependent change in metabolite composition in the skin, which resulted in binding of a part of metabolites to skin tissue, and an increase in the proportion of bound metabolites for up to 24 hours post-dose. The excretion study in rats (4.2.2.5-1) showed that approximately 5% of the administered radioactivity remained in the carcass even at 168 hours post-dose. Aside from the radioactivity reabsorbed via enterohepatic circulation, a higher proportion of radioactivity may remain in the skin because skin weight accounts for 22% of body weight, i.e. occupies a higher proportion than other tissues (Galtier P, *et al*., *Drug Metab. Dispos*. 1979;7(6):429-34). Based on the above, the applicant considered that in rats, topiroxostat was rapidly absorbed and its plasma concentration was eliminated over time, while a part of radioactivity transferred from the plasma to the skin was eliminated only after metabolism and skin tissue binding, resulting in a slower increase followed by a slower decrease in radioactivity levels in the skin than in the plasma. Analysis of likely skin-bound components was attempted, but failed to identify the structures and types. Given that topiroxostat has no phototoxicity, and that overall toxicity studies revealed no findings of skin toxicity, the metabolites remaining in the skin are unlikely to cause toxicity. Furthermore, prolonged retention of metabolites in the skin, as observed in rats, is extremely unlikely to occur in humans because a human mass-balance study (Study FYX-051-137) has shown that the total urinary and fecal excretion in humans was 101.6%, i.e. complete recovery, at 96 hours post-dose.

PMDA accepted the above response because, although the higher radioactivity level in the skin than in

the plasma and persistent residues of radioactivity in the skin in rats had not been explained in detail, persistent topiroxostat residues were not suggested in humans. PMDA will comprehensively discuss skin-related safety in "3.(ii).B.(2) Melanin affinity."

3.(ii).B.(2) Melanin affinity

The distribution study in pigmented rats (4.2.2.3-2) showed that the radioactivity level was 19 times higher in the eye than in the plasma at 24 hours post-dose, and that the $T_{1/2}$ was 101 and 68.9 hours in the pigmented skin and eye, respectively, indicating slower elimination than in other tissues (the $T_{1/2}$ of radioactivity in the plasma was 21.9 hours). Results suggested melanin affinity of topiroxostat. Based on the findings, PMDA asked the applicant to explain the relevance of melanin affinity of topiroxostat to humans

The applicant responded as follows:

The investigation using pigmented rats showed higher radioactivity level in melanin-containing tissues such as the eye and pigmented skin than white rats, suggesting melanin binding of topiroxostat. However, persistent residues of topiroxostat or its metabolites are unlikely because the radioactivity level decreased over time. In addition, no abnormality was observed in the ocular tissues or skin in the 4- and 13-week repeated oral dose toxicity studies in dogs (4.2.3.2-4 and 4.2.3.2-5) and in the 13- and 52-week repeated oral dose toxicity studies in monkeys (4.2.3.2-6 and 4.2.3.2-7), and topiroxostat was negative in a phototoxicity study using pigmented rats. Regarding the effects on humans, a pooled double-blind study analysis[10] revealed that the incidence of adverse events in the System Organ Class (SOC) "Eye disorders" was 3.7% in the placebo group (5 of 135 subjects; allergic conjunctivitis in 4 subjects, vitreous haemorrhage in 1 subject), 1.1% in the topiroxostat group (all doses pooled)[12] (5 of 465 subjects; asthenopia, cataract, conjunctival haemorrhage, allergic conjunctivitis, and posterior capsule opacification in 1 subject each), 1.5% in the topiroxostat maintenance-phase dose group[13] (5 of 328 subjects; asthenopia, cataract, conjunctival haemorrhage, allergic conjunctivitis, and posterior capsule opacification in 1 subject each), and 0.7% in the allopurinol group[14] (1 of 144 subjects, asthenopia in 1 subject). All events were mild except for moderate cataract. Therefore, the applicant considers that clinical studies have shown no effect of topiroxostat administration on the eye.

Regarding the effect on the skin, the pooled double-blind study analysis[10] revealed that the incidence of adverse events in the SOC "Skin and subcutaneous tissue disorders" was 6.7% in the placebo group (9 of 135 subjects[15]), 4.5% in the topiroxostat group (all doses pooled)[12] (21 of 465 subjects), 5.5% in the topiroxostat maintenance-phase dose group[13] (18 of 328 patients), and 4.9% in the allopurinol group[14] (7 of 144 subjects[16]). All events in the placebo and allopurinol groups were mild; among

[12] Topiroxostat 40, 60, 80, 120, and 160 mg/day groups
[13] Topiroxostat 120 and 160 mg/day groups
[14] Allopurinol 200 mg/day group
[15] Eczema in 4 subjects, hyperkeratosis in 2 subjects, dry skin, erythema, and rash in 1 subject each
[16] Eczema in 2 subjects, rash in 2 subjects, eczema/pruritus in 1 subject, urticaria and dermatitis in 1 subject each

adverse events in the topiroxostat group, 3.9% (18 of 465 subjects[17]) were mild and 0.6% (3 of 465 subjects[18]) were moderate, but no severe adverse event was observed. A pooled analysis of long-term treatment studies in human patients (pooled long-term treatment study analysis)[19] revealed that the incidence of adverse events in the SOC "Skin and subcutaneous tissue disorders" was 9.4% (34 of 361 subjects) in the topiroxostat group among these adverse events, 8.6% (31 of 361 subjects[20]) were mild and 0.8% (3 of 361 subjects[21]) were moderate, but no severe adverse event was observed. The incidence of moderate or more severe events showed no tendency to increase with prolonged treatment. Based on the above, the effects on the skin are unlikely to be a clinical concern.

PMDA accepted the above explanation in terms of non-clinical studies and human eye safety. However, PMDA will further discuss human skin safety in the clinical section because skin-related adverse drug reactions have been reported for allopurinol, a drug in the same class [see "4.(iii).B.(3).4) Cutaneous adverse events"].

3.(iii) Summary of toxicology studies

3.(iii).A Summary of the submitted data

Single dose toxicity studies, repeated dose toxicity studies, genotoxicity studies, carcinogenicity studies, reproductive and developmental toxicity studies, and other toxicity studies (antigenicity study, photosafety study, and mechanism of toxicity study) were conducted. The study on the mechanism of toxicity was considered a reference study, since it was not conducted in compliance with the Good Laboratory Practice (GLP).

3.(iii).A.(1) Single-dose toxicity (4.2.3.1-1 to 6)

Oral dose studies in CD-1 mice, CD (SD) rats, beagle dogs, and cynomolgus monkeys and intraperitoneal administration studies in CD-1 mice and CD (SD) rats were conducted to evaluate single dose toxicity. The approximate lethal dose was determined to be: >2000 mg/kg in mice, dogs, and monkeys and >750 mg/kg in rats after oral administration; and 300 mg/kg in mice and 500 to 600 mg/kg in rats after intraperitoneal administration. Toxicity findings included white discoloration of the kidney in rats after oral administration. Bloody stools and loose stools were observed in dogs for several days, but necropsy at 2 weeks post-dose revealed no abnormality in the gastrointestinal tract. Findings in intraperitoneal administration studies included a diminished or white discolored kidney and splenomegaly in mice and abnormal gait, decreased spontaneous movement, lacrimation, piloerection, hunched posture, white discoloration or small white spots of the liver, white discoloration of the kidney, and splenomegaly in rats.

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17 Eczema in 6 subjects, rash in 3 subjects, dermatitis, dermatitis contact and pruritus in 2 subjects each, dandruff, hyperkeratosis, and xeroderma in 1 subject each

18 Dermatitis, drug eruption, and eczema in 1 subject each

19 Pooled analysis of Studies FYX-051-332 and FY1002

20 Eczema in 6 subjects, rash in 5 subjects, urticaria in 4 subjects, dermatitis contact in 3 subjects, pruritus in 2 subjects, eczema/urticaria, eczema asteatotic/urticaria, eczema/dermatitis contact, erythema/dermatitis contact, urticaria cholinergic/eczema/urticaria, erythema, cold sweat, dermatitis, drug eruption, heat rash, and xeroderma in 1 subject each

21 Dermatitis allergic, erythema multiforme, and urticaria in 1 subject each

3.(iii).A.(2) Repeat-dose toxicity

Oral administration studies were conducted in rats (4, 13, and 26 weeks), dogs (4 and 13 weeks), and monkeys (13 and 52 weeks) to evaluate repeated dose toxicity. The main toxicity of topiroxostat administration was renal disorder, probably due to deposition of xanthine crystals. Renal disorder was observed in rats and dogs but not in monkeys even after long-term administration. Toxicity findings in the kidney showed reversibility after a recovery period. Comparison of AUC[7] values for unchanged topiroxostat at the no-observed-adverse-effect level (NOAEL) and at the maximum recommended clinical dose yielded a safety margin of <1-fold (0.06-fold) in rats (26 weeks), approximately 2-fold in dogs (13 weeks), and ≥76-fold in monkeys (52 weeks). The applicant discussed that the species differences in toxicity were mainly due to differences in the turnover rate of purine metabolism (4.2.3.7-10, reference data).

3.(iii).A.(2).1) Four-week repeated oral dose toxicity study in rats (4.2.3.2-1)

A study of once-daily, 4-week oral administration of 0 (vehicle[4]), 0.3, 1, or 3 mg/kg/day of topiroxostat was conducted in male and female CD (SD) rats. The results showed an increase in urinary output, basophilic changes or enlargement of renal tubules or collecting duct, stromal cell infiltration or connective tissue hyperplasia in the renal papilla, and hyperplasia of the renal papilla or renal pelvic epithelium in the ≥1 mg/kg/day groups and suppressed body weight gain, reduced food intake, emaciation, piloerection, hunched posture, increases in urea nitrogen and creatinine in blood, a reduced urine specific gravity, epithelial cells in urinary sediment, renal changes including an increase in kidney weight, enlargement or swelling of the kidney, granular changes, and white discoloration, and hepatocyte changes in the liver accompanied by a decrease in glycogen levels in the 3 mg/kg/day group. Scarring of kidney lesions was observed after a 4-week recovery period, but decreased toxicity in the kidney indicated reversibility.

3.(iii).A.(2).2) Thirteen-week repeated oral dose toxicity study in rats (4.2.3.2-2)

A study of once-daily, 13-week oral administration of 0 (vehicle[4]), 0.3, 1, or 3 mg/kg/day of topiroxostat was conducted in male and female CD (SD) rats. The results showed yellowish white granular material in the bladder and renal changes including white or yellowish white foci, a rough surface, yellowish white granular material on the cut surface, mononuclear cell infiltration in the cortex or stromal fibrosis, basophilic changes or dilatation of the renal tubules, foreign bodies or cell debris in the collecting duct, and hyperplasia of the renal papilla or renal pelvic epithelium in the ≥1 mg/kg/day groups. In the 3 mg/kg/day group, a transient suppression of body weight gain, high levels of urea and creatinine in blood, yellowish white granular material in the urethra, stromal edema in the renal papilla, mononuclear cell infiltration in the renal pelvic mucosa, etc. were observed. The NOAEL was determined to be 0.3 mg/kg/day. The applicant attributed the nephrotoxicity of topiroxostat administration to deposition of xanthine crystals due to the fact that the major component of the yellowish white granular material was identified as xanthine by LC-MS/MS.

3.(iii).A.(2).3) Twenty-six-week repeated oral dose toxicity study in rats (4.2.3.2-3)

A study of once-daily, 26-week oral administration of 0 (vehicle[4]), 0.04, 0.2, or 1 mg/kg/day of topiroxostat was conducted in male and female CD (SD) rats. The results showed yellow granular material in urinary sediment and on the cut surface of the kidney in the ≥0.2 mg/kg/day groups, while changes in the kidney were observed in the 1 mg/kg/day group, probably due to xanthine crystal deposition, similarly to the findings in the 13-week oral dose study. In addition, 1 of 14 male rats in the 1 mg/kg/day group died because of general physical deterioration caused by renal failure, and surviving male rats in the 1 mg/kg/day group showed an increased urinary output, decreased urine specific gravity and osmolality, and high levels of white blood cells in urinary sediment, blood urea nitrogen, and creatinine. No new toxic changes were observed in the prolonged treatment in comparison with the 13-week oral dose study. Given that the yellow granular material observed in the 0.2 mg/kg/group was not accompanied by toxic effects, the NOAEL was determined to be 0.2 mg/kg/day.

3.(iii).A.(2).4) Four-week repeat-dose toxicity study in dogs (4.2.3.2-4)

A study of once-daily, 4-week oral administration of 0 (vehicle[4]), 3, 10, or 30 mg/kg/day of topiroxostat was conducted in male and female beagle dogs. The results showed increased linear scar lesions and minute renal pelvic calculi in the kidney in the ≥10 mg/kg/day groups and swelling of the kidney in the 30 mg/kg/day groups. The renal pelvic calculi continued to be observed after a 4-week recovery period.

3.(iii).A.(2).5) Thirteen-week repeat-dose toxicity studies in dogs (4.2.3.2-5, 4.2.3.2-8, reference data)

A study of once-daily, 13-week oral administration of 0 (vehicle[4]), 10, 30, or 100 mg/kg/day of topiroxostat was conducted in male and female beagle dogs. The results showed: minute yellow granular material in urinary sediment in the ≥10 mg/kg/day groups; abnormal stool color (contamination of yellowish white or white material), probably due to unabsorbed topiroxostat, and hyperplasia of the renal pelvic and papillary epithelia in the kidney in the ≥30 mg/kg/day groups; and increased blood creatinine, deposition of yellowish white granular material in the kidney, large pelvic calculi, dilatation of the distal tubules, and degeneration or necrosis in the distal tubule epithelium in the 100 mg/kg/day group. Single cell necrosis of the renal papilla, hemorrhage or inflammatory cell infiltration in the soft tissue surrounding the renal pelvis, and hemorrhage in the cortex and medulla were also observed in 100 mg/kg/day group, and they were attributed to the physical stimulation by the large calculi. After a 4-week recovery period, deposition of yellowish white granular material and pelvic calculi continued to be observed in the kidney in the 100 mg/kg/day group, but other changes were reversible. The NOAEL was determined to be 10 mg/kg/day. Given that the major component of the yellowish white granular material was identified as xanthine by LC-MS/MS in the study on the mechanism of nephrotoxicity in dogs (4.2.3.7-5, reference data), the applicant attributed the nephrotoxicity of topiroxostat administration to deposition of xanthine crystals.

3.(iii).A.(2).6) Thirteen-week repeated oral dose toxicity studies in monkeys (4.2.3.2-6, 4.2.3.2-8, reference data)

A study of once-daily, 13-week oral administration of 0 (vehicle[4]), 10, 30, or 100 mg/kg/day of topiroxostat was conducted in male and female cynomolgus monkeys. The results showed abnormal stool color (yellowish white) in the 100 mg/kg/day group, but no other abnormality was found. The NOAEL was determined to be ≥100 mg/kg/day.

3.(iii).A.(2).7) Fifty-two-week repeated oral dose toxicity studies in monkeys (4.2.3.2-7)

A study of once-daily, 52-week oral administration of 0 (vehicle[4]), 30, 100, or 300 mg/kg/day of topiroxostat was conducted in male and female cynomolgus monkeys. The results showed abnormal stool color (white, yellowish white, or grayish white) in the 300 mg/kg/day group, but no other abnormality was found. The NOAEL was determined to be ≥300 mg/kg/day.

3.(iii).A.(3) Genotoxicity

Genotoxicity was evaluated in a bacterial reverse mutation assay (4.2.3.3-1), a chromosomal aberration assay in cultured mammalian cells (Chinese hamster lung-derived fibroblasts) (4.2.3.3-2), and an oral bone marrow micronucleus assay in rats (4.2.3.3-3), in none of which topiroxostat showed genotoxicity.

3.(iii).A.(4) Carcinogenicity

Carcinogenicity was evaluated in 2-year oral dose studies in mice and rats. Tumors developed in both animal species (mice, mammary adenocarcinoma; rats, transitional cell papilloma/papillary carcinoma in the kidney and bladder, transitional cell carcinoma in the ureter, renal cell carcinoma and angiosarcoma in the kidney, follicular cell adenoma in the thyroid), secondary to chronic renal impairment probably due to xanthine crystal deposition. Comparison of the exposure (AUC)[7] to unchanged topiroxostat at the non-carcinogenic doses in mice and rats and at the maximum recommended clinical dose yielded a safety margin of <1-fold in both animal species. However, the applicant has considered that the observed tumorigenesis is not relevant to humans because xanthine crystal deposition is pronounced in rodents in comparison with other animal species including humans.

3.(iii).A.(4).1) Carcinogenicity study in mice (4.2.3.4-2)

A study of once-daily, 2-year oral administration of 0 (vehicle[4]), 0.3, 1, or 3 mg/kg/day of topiroxostat was conducted in male and female B6C3F1 mice. The results showed adenocarcinoma due to infection with mouse mammary gland tumor virus (B-type virions) in the mammary glands of females in all groups including the control group (12 of 50 animals in the control group, 11 of 50 in the 0.3 mg/kg/day group, 15 of 50 animals in the 1 mg/kg/ day group, and 24 of 50 animals in the 3 mg/kg/day group). The incidence was higher in the 3 mg/kg/day group, in which general physical deterioration associated with serious chronic renal impairment was observed. Based on the finding, the applicant considered that tumor virus infection enhanced tumorigenesis.

Non-neoplastic lesions observed included chronic renal impairment and simple transitional cell hyperplasia in the renal pelvis and bladder, both of which were probably due to physical stimulation by deposited xanthine crystals or calculi, in the 3 mg/kg/day group.

3.(iii).A.(4).2) Carcinogenicity study in rats (4.2.3.4-4)

A study of once-daily, 2-year oral administration of 0 (vehicle[4]), 0.3, 1, or 3 mg/kg/day of topiroxostat was conducted in male and female F344 rats. The results showed: transitional cell papilloma in the bladder of males in the ≥0.3 mg/kg/day groups (0 of 50 animals in the control group, 1 of 49 animals in the 0.3 mg/kg/day group, 1 of 49 in the 1 mg/kg/day group, and 3 of 50 animals in the 3 mg/kg/day group); transitional cell carcinoma in the bladder of males in the ≥1 mg/kg/day groups (0 of 50 animals, 0 of 49 animals, 2 of 49 animals, and 7 of 50 animals, respectively); transitional cell papilloma (male, 0 of 50 animals, 0 of 50 animals, 0 of 50 animals, and 2 of 50 animals, respectively; female, 0 of 50 animals, 0 of 50 animals, 0 of 50 animals, and 1 of 50 animals, respectively) and papillary angiosarcoma (male, 0 of 50 animals, 0 of 50 animals, 0 of 50 animals, and 7 of 50 animals, respectively; female, 0 of 50 animals, 0 of 50 animals, 0 of 50 animals, and 3 of 50 animals, respectively) in the kidney of males and females in the 3 mg/kg/day group; transitional cell carcinoma in the kidney of males in the 3 mg/kg/day group (0 of 50 animals, 0 of 50 animals, 0 of 50 animals, and 2 of 50 animals, respectively); and renal cell carcinoma (0 of 50 animals, 0 of 50 animals, 0 of 50 animals, and 1 of 50 animals, respectively) and transitional cell carcinoma in the ureter (0 of 50 animals, 0 of 49 animals, 0 of 50 animals, and 1 of 50 animals, respectively) in females in the 3 mg/kg/day group. In addition, males in the 3 mg/kg/day group showed follicular cell adenoma in the thyroid gland (0 of 50 animals, 1 of 50 animals, 0 of 50 animals, and 4 of 49 animals, respectively). The applicant attributed the observed tumorigenesis to the physical stimulation by deposited xanthine crystals/calculi or to serious chronic renal impairment.

Non-neoplastic lesions observed included crystal deposition and calculus formation in the renal tubules and urinary tract, transitional cell hyperplasia in the bladder (bladder apex, in particular ventral aspect) and urinary tract, diffuse or localized hyperplasia of thyroid follicular cells, diffuse hyperplasia of parathyroid gland, arterial dilatation, mineral deposition due to metastatic calcification (arteries, kidney, heart, lung, stomach, eye cornea, vas deferens, mammary gland, skeletal muscle, arterioles in various organs and tissues, smooth muscle fibers), fibrous osteodystrophy (sternum, femur), arteriolosclerosis in the kidney, exacerbation of chronic nephropathy or cardiomyopathy, polyarteritis (tongue, duodenum, cecum, colon, mesentery, liver, kidney, testis, pancreas), sclerosis of arterial intima, and aneurysm (pancreas, spermatic cord).

3.(iii).A.(5) Reproductive and developmental toxicity

Reproductive and developmental toxicity was assessed in fertility and pre-implantation early embryonic development studies in rats, embryo-fetal development studies in rats and rabbits, and a pre- and postnatal development and maternal function study in rats. As a result, administration of topiroxostat showed no teratogenicity, and comparison of the exposure (AUC)[7] to unchanged

topiroxostat at the NOAEL for embryo-fetal development in rabbits and at the maximum recommended clinical dose yielded a safety margin of ≥77-fold. In rats, topiroxostat has been shown to cross the placenta (4.2.2.3-7) and to be excreted in milk (4.2.2.5-2).

3.(iii).A.(5).1) Fertility and early embryonic development to implantation studies in rats (4.2.3.5-1, 4.2.3.2-8, reference data)

A study of once-daily oral administration of 0 (vehicle[4]), 1, 3, or 10 mg/kg/day of topiroxostat was conducted in male and female CD (SD) rats. Males were treated for 28 days prior to mating and until the day before necropsy, and females were treated for 14 days prior to mating and until gestation day 6. The results showed: white foci and a rough surface of the kidney in the ≥1 mg/kg/day groups, death (male only), suppressed body weight gain, reduced food intake, decreased spontaneous movement, traces of red nasal discharge, unkempt fur, yellowish white granular material in the renal pelvis in the ≥3 mg/kg/day groups, and emaciation, piloerection, and decreased body temperature in the 10 mg/kg/day group, but fertility and early embryogenesis were not affected. The NOAEL was determined to be <1 mg/kg/day for general toxicity in parental animals and 10 mg/kg/day for parental fertility and offspring development.

3.(iii).A.(5).2) Embryo-fetal development

(a) Study in rats (4.2.3.5-3)

A study of once-daily oral administration, from gestation day 6 to 17, of 0 (vehicle[4]), 3, 10, or 30 mg/kg/day of topiroxostat was conducted in pregnant CD (SD) rats. The results showed, in maternal animals: white foci in the kidney in the ≥3 mg/kg/day groups; suppressed body weight gain, a rough kidney surface, and yellowish white granular material on the renal pelvis and the cut surface of the kidney in the ≥10 mg/kg/day groups; and death, decreased spontaneous movement, decreased fecal output, emaciation, traces of red nasal discharge, perineal staining by urine, and swelling of the kidney in the 30 mg/kg/day group, but no effects were observed in embryos and fetuses. The NOAEL was determined to be <3 mg/kg/day for general toxicity in maternal animals and 30 mg/kg/day for maternal reproductive function and offspring development.

(b) Study in rabbits (4.2.3.5-5)

A study of once-daily oral administration, from gestation day 6 to 18, of 0 (vehicle[4]), 3, 10, or 30 mg/kg/day of topiroxostat was conducted in pregnant NZW rabbits. The results showed no effect on maternal animals, embryos, or fetuses. The NOAEL was determined to be 30 mg/kg/day for maternal general toxicity, maternal reproductive function, and offspring development.

3.(iii).A.(5).3) Pre- and postnatal development, including maternal function study in rats (4.2.3.5-6)

A study of once-daily oral administration, from gestation day 6 to lactation day 21, of 0 (vehicle[4]), 0.3, 1, or 3 mg/kg/day of topiroxostat was conducted in pregnant CD (SD) rats. The results showed, in maternal animals (F0): suppressed body weight gain and white foci on the kidney surface during

pregnancy in the ≥1 mg/kg/day groups and death during parturition, a lower body weight during the period from gestation day 18 to lactation day 14, lower food intake during the lactation period, abandonment of lactation resulting in death of all pups, a rough kidney surface, white foci on the cut surface of the kidney, and yellowish white material on the surface and cut surface of the kidney and renal pelvis in the 3 mg/kg/day group. A low body weight was observed in F1 pups of the 3 mg/kg/day group, but no effects of topiroxostat administration were observed in F2 pups. One of 19 maternal animals (F0) in the 1 mg/kg/day group abandoned lactation, resulting in death of all pups, but the applicant considered this event to be an incidental finding because this was within the range of background data at the study facility. The NOAEL was determined to be 0.3 mg/kg/day for general toxicity in maternal animals and 1 mg/kg/day for maternal reproductive function and offspring development.

3.(iii).A.(6) Other toxicity studies

3.(iii).A.(6).1) Antigenicity

(a) Study in mice (4.2.3.7-1)

Male BALB/c and C3H/He mice were sensitized either by once-daily, 15-day oral administration of 1 or 5 mg/kg/day of topiroxostat suspended in vehicle[4] or by 3 once-weekly intraperitoneal doses of 5 mg/kg/day of topiroxostat with concomitant saline 2% aluminum hydroxide gel suspension, and were tested for heterologous passive cutaneous anaphylaxis at 14 days after the final sensitization in each group. The results showed no positive reaction, and topiroxostat was considered to have no antigenicity in mice.

(b) Study in guinea pigs (4.2.3.7-2)

Male Hartley guinea pigs were sensitized either by once-daily, 15-day oral administration of 1 or 5 mg/kg/day of topiroxostat suspended in vehicle[4] or by 3 once-weekly subcutaneous doses of 5 mg/kg/day of topiroxostat with concomitant Complete Freund's Adjuvant, and were tested for systemic anaphylaxis and homologous passive cutaneous anaphylaxis at 14 days after the final sensitization in each group. The results showed no positive reaction, and topiroxostat was considered to have no antigenicity in guinea pigs.

3.(iii).A.(6).2) Photosafety study (4.2.3.7-3)

Male Long-Evans rats were given a single oral dose of 0 (vehicle[4]), 30, 100, or 300 mg/kg/day of topiroxostat, and were irradiated by long wavelength ultraviolet light (approximately 10 J/cm^2) starting at 30 minutes after treatment. Photosafety was assessed by gross observation of the auricle and skin, measurement of auricular thickness, ophthalmological examination, and histopathological examination of the auricle and skin. The results showed no abnormality, and topiroxostat was considered to have no phototoxicity in pigmented rats.

3.(iii).A.(6).3) Studies on the mechanism of toxicity

(a) Study on the mechanism of nephrotoxicity in rats (4.2.3.7-4, reference data)

Following 4 weeks of once-daily oral administration of 0 (vehicle[4]), 0.3, 1, or 3 mg/kg/day of either topiroxostat or topiroxostat N-oxide to male CD (SD) rats, the effect of topiroxostat N-oxide, a major metabolite[22] of topiroxostat, on the rat kidney was studied. The results in topiroxostat groups showed increases in urine output and urine β-N-acetyl-D-glucosaminidase (NAG) at ≥1 mg/kg/day and decreased urine osmolality at 3 mg/kg/day, which suggested that topiroxostat administration impaired urinary concentration (impaired function of the distal tubule and the collecting duct) and affected the proximal tubule. Interstitial nephritis and hyperplasia of epithelial cells in the renal papilla and pelvis were also observed at ≥1 mg/kg/day. Meanwhile, the findings in topiroxostat N-oxide groups included hyperplasia of epithelial cells in the renal papilla at ≥1 mg/kg/day and increased urine output, decreased urine osmolarity, increased urine NAG, and interstitial nephritis at 3 mg/kg/day. In topiroxostat N-oxide groups, interstitial nephritis was milder than in topiroxostat groups.

In an additional study, allopurinol[23] was orally administered once daily at 0 (vehicle[4]), 30, or 100 mg/kg/day for 4 weeks. Renal histopathological changes observed in the ≥30 mg/kg/day allopurinol groups were similar to those observed after topiroxostat administration. The 100 mg/kg/day group showed increased urine output, decreased urine osmolality, and increased urine NAG.

These study results showed that the nephrotoxicity of topiroxostat N-oxide and allopurinol has the same profile as that of topiroxostat, and therefore the applicant has concluded that the observed toxic changes are common to XOR inhibitors.

(b) Study on the mechanism of nephrotoxicity in dogs (4.2.3.7-5, reference data)

Following 4 weeks of once-daily oral administration of 0 (vehicle[4]) or 100 mg/kg/day of topiroxostat to male beagle dogs, the effect of topiroxostat on dog renal function was studied. As a result, the main component of renal deposits as identified as xanthine by LC-MS/MS. Histopathological examination of the kidney showed foreign bodies in the renal pelvic cavity and mild hyperplasia of epithelial cells in the renal papilla, but urinalysis findings were not suggestive of abnormal renal function.

(c) Effect of citrate on nephrotoxicity in rats (4.2.3.7-6, reference data)

To study the association between xanthine crystal deposition and nephrotoxicity in rats treated with topiroxostat, rats received topiroxostat and concomitant citrate, a urine alkalizing agent, and reduction of nephrotoxicity by urine alkalization was assessed.

Male CD (SD) rats received once-daily, 4-week oral administration of 0 (vehicle[4]), 1, or 3 mg/kg/day of topiroxostat with or without concomitant citrate of 4000 to 5000 mg/kg/day. After administration of

[22] Major metabolites are topiroxostat N-oxide in rats and glucuronide conjugates in humans (Study FYX-051-111).

[23] Dose of allopurinol was calculated on the basis that it has approximately 1/30 the uric acid-lowering activity of topiroxostat.

topiroxostat alone, mild to moderate interstitial nephritis occurred in the 1 mg/kg/day group (6 of 8 animals) and moderate or severe interstitial nephritis occurred in the 3 mg/kg/day group (8 of 8 animals). However, after administration of topiroxostat in combination with citrate, only mild interstitial nephritis was observed in the 3 mg/kg/day group (1 of 8 animals), indicating suppression of topiroxostat nephrotoxicity by concomitant administration of citrate. Urine pH was 7 after administration of topiroxostat alone, but increased to 8 when citrate was added. It was inferred that the concomitant administration of citrate caused the urine pH in the tubular lumen to become slightly alkaline and the resulting increase in the solubility of xanthine suppressed deposition of xanthine crystals, thereby suppressing the drug's nephrotoxicity. Based on the above, the applicant attributed topiroxostat nephrotoxicity to deposition of xanthine crystals in the kidney.

3.(iii).A.(6).3).(d) Study of nephrotoxicity suppression by citrate in rats: a 52-week study (4.2.3.7-7, reference data)

To study the association between xanthine crystal deposition and lesions in the urinary organs (kidney, bladder, and ureter) of rats treated with topiroxostat, rats received long-term administration (52 weeks) of topiroxostat with concomitant citrate, a urine-alkalizing agent, and prevention of lesions in the urinary organs by urine alkalization was assessed.

Male F344 rats received once-daily, 52-week oral administration of 0 (vehicle[4]) or 3 mg/kg/day of topiroxostat with or without concomitant 3500 mg/kg/day of citrate. The results showed white turbid urine, red urine (haematuria), high levels of blood creatinine and urea nitrogen, grape-bunch-like crystals in urinary sediment, increased urine output, decreased urine osmolarity, and decreased kidney weight in rats that received topiroxostat alone. Pathological changes were observed in the kidney (interstitial nephritis characterized by gross changes including atrophy, rough surface, and white spots, and microscopic changes including basophilic changes in the renal tubules, cell debris in the lumen of renal tubules, calculi in the renal pelvis, fibrosis, and transitional cell hyperplasia), bladder (calculi, cell infiltration, transitional cell hyperplasia [simple hyperplasia and papillary hyperplasia]), and ureter (calculi, transitional cell hyperplasia). These changes were not observed when topiroxostat was combined with citrate.

3.(iii).A.(6).3).(e) Effects on growth of vascular endothelial cells (4.2.3.7-8 to 9, reference data)

Given that the rat carcinogenicity study had shown angiosarcoma localized to the renal papilla, the effect of topiroxostat on the proliferative activity of vascular endothelial cells was studied.

Normal human umbilical vein endothelial cells (HUVEC) were incubated with topiroxostat at a concentration range from 0 (vehicle[24]) to 30 μmol/L (a concentration approximately 10 times the C_{max} [608.5 ng/mL] at the maximum recommended clinical dose) for approximately 48 hours to study cell proliferative activity and cytotoxicity. The results showed decreased cell viability at 30 μmol/L, suggestive of mild cytotoxicity, but cell proliferation was not enhanced at any concentration.

[24] PBS solution containing 0.1% DMSO and 0.1% BSA

3.(iii).A.(6).3).(f) Amounts of purine metabolites in urine of different animal species (4.2.3.7-10, reference data)

Daily urine excretion of purine metabolites (total amounts of hypoxanthine, xanthine, uric acid, and allantoin) was measured by 24-hour urine collection in rats, dogs, monkeys, and humans. The results showed the following urine excretion of purine metabolites per body weight: 1934.7 μmol/kg/day in rats, 402.8 μmol/kg/day in dogs, 62.0 μmol/kg/day in monkeys, and 52.8 μmol/kg/day in humans. The applicant attributed the species differences in toxicity mainly to differences in the turnover rate of purine metabolism because species-specific excretion normalized to the human value was 36.6 for rats, 7.6 for dogs, and 1.2 for monkeys.

3.(iii).A.(6).3).(g) Solubility of xanthine in urine of different animal species (4.2.3.7-11, reference data)

The effect of urine pH on the solubility of xanthine (37°C) was studied by adding xanthine to the urine of rats, dogs, monkeys, and humans. The results showed that xanthine solubility was only slightly higher at pH 7 than at pH 5 in the urine of all animal species (xanthine solubility in rat urine was 155 mg/dL at pH 5 and 167 mg/dL at pH 7), but it was markedly higher at pH ≥8 than at pH ≤7. Xanthine solubility at pH up to 8 was similar among animal species. Given that urine pH is 6.7 in rats, 7.8 in dogs, 9.0 in monkeys, and 5.5 in humans, the applicant inferred that urine solubility of xanthine is higher in dogs and monkeys, which have higher urine pH, than in rats and humans.

3.(iii).B Outline of the review by PMDA

PMDA has reviewed the following sections 3.(iii).B.(1) to (3), and accepts the applicant's response from a toxicological point of view. However, PMDA will further discuss nephrotoxicity and hepatotoxicity of topiroxostat in the clinical section [see "4.(iii).B.(3).2) Hepatic impairment" and "4.(iii).B.(3).3) Kidney or bladder-related adverse events "].

3.(iii).B.(1) Nephrotoxicity

PMDA asked the applicant to discuss safety in humans with regard to the nephrotoxicity of topiroxostat, attributed to renal deposition of xanthine crystals due to XOR inhibition, envisaging diseases that cause uric acid to be overproduced.

The applicant responded as follows:

Following 7 days of repeated, twice-daily oral administration of 80 mg (160 mg/day, the maximum recommended clinical dose) of topiroxostat, the maximum xanthine concentration was 11.54 mg/dL in random urine samples taken during the 12 hours post-dose. The *in vitro* solubility of xanthine in human urine was 124 mg/dL at pH 5, 37°C. Therefore, an approximately 10-fold difference is estimated between the solubility of xanthine in urine and the maximum urine concentration of xanthine after administration of topiroxostat at the maximum recommended clinical dose. Moreover, urine sediment examination showed no xanthine crystals in random urine samples after administration

of topiroxostat at the maximum recommended clinical dose. Based on the above, it is unlikely that deposition of urine xanthine crystals would occur in humans treated with topiroxostat, or resulting nephrotoxicity would raise major concerns. On the other hand, xanthine calculus formation has been reported[25] in association with allopurinol administration in patients with Lesch-Nyhan syndrome, a disease that causes hyperuricaemia due to diminished function of the purine salvage pathway resulting from a genetic defect of hypoxanthine-guanine phosphoribosyltransferase, or with hyperuricaemia due to myeloid tumor. Therefore, it is inferred that, when massive cell death occurs due to the above diseases or anticancer chemotherapy, the administration of allopurinol would lead to urinary excretion of xanthine exceeding its solubility in urine, resulting in xanthine calculus formation. Although the possibility of xanthine crystal deposition induced by topiroxostat administration cannot be ruled out, the risk is estimated to be similar between topiroxostat and other XOR inhibitors, such as allopurinol. This is because topiroxostat had little effect on the enzymes of purine and pyrimidine metabolism (4.2.1.1-5, 6), and the increase in urinary excretion of hypoxanthine and xanthine in association with topiroxostat administration can be explained by inhibition of uric acid biosynthesis. Nephrotoxicity is considered to be avoidable by sufficient water intake and urine alkalization, as recommended for urinary tract management in patients with gout or hyperuricaemia in the "Guideline for the Management of Hyperuricaemia and Gout, Second Edition" (edited by the Guideline Revision Committee of the Japanese Society of Gout and Nucleic Acid Metabolism, 2010).

3.(iii).B.(2) Hepatotoxicity

PMDA asked the applicant to discuss hepatic impairment after topiroxostat administration reported as adverse drug reactions in human clinical studies, envisaging the possibility of idiosyncratic drug toxicity (IDT), although toxicity studies have shown no hepatotoxicity in any animal species.

The applicant responded as follows:

As in the cases of other drugs in the same class (febuxostat and allopurinol), toxicity studies of topiroxostat have shown no findings suggestive of hepatotoxicity, while clinical studies of topiroxostat showed adverse drug reactions related to hepatic impairment, as in the case of febuxostat, and fulminant hepatitis has been reported to occur in association with allopurinol. Nevertheless, species differences in hepatotoxicity have not been explained for any of these drugs. In regard to mitochondrial toxicity, a proposed mechanism of IDT, topiroxostat was studied for its effects on the activity of enzymatic complexes I, II, and III and of palmitoyl-CoA dehydrogenase, mediating β oxidation of fatty acids, among mitochondrial enzymes involved in cell survival and functioning. The results showed no appreciable inhibition: approximately 4.5% to 12.8% when topiroxostat was at a high concentration of 100 μmol/L (approximately 40 times higher than C_{max}, 608.5 ng/mL [2.45 μmol/L] at the maximum recommended clinical dose). Given that the mechanism of IDT is yet to be explained in detail, that the possibility of topiroxostat-induced IDT in humans cannot be ruled out, and that clinical studies have shown adverse drug reactions related to hepatic function in

[25] Pais VM Jr, *et al., Urology*, 2006;67:1084.e9-11, Brock WA, *et al., J Urol*, 1983;130:157-9, Kranen S, *et al., J Urol*, 1985;133:658-9, Ablin A, *et al., Metabolism*, 1972;21:771-8, Band PR, *et al., N Engl J Med*, 1970;283:354-7

association with topiroxostat administration, the applicant will advise caution that hepatic function monitoring is needed during clinical use of topiroxostat.

3.(iii).B.(3) Carcinogenicity

PMDA understands the applicant's view that, among the tumors suspected to be related to topiroxostat administration in carcinogenicity studies, epithelial tumors in rat kidney, bladder, and ureter were caused by tissue injury due to xanthine crystals forming at the corresponding sites. PMDA, however, requested the applicant to explain the pathogenesis of breast adenocarcinoma in mice, to which the relationship of xanthine calculus formation is not sufficiently clear, and renal angiosarcoma and thyroid gland follicular cell tumor in rats, and also to discuss safety in humans.

The applicant responded as follows:

In the mouse carcinogenicity study, breast adenocarcinoma increased throughout the study including the control group, with a significant increase in the high-dose topiroxostat groups. Conceivable causes involve infection with mouse mammary tumor virus (MMTV) and general physical and functional deterioration accompanying chronic renal impairment associated with topiroxostat administration. In this study, electron microscopy of the mammary tissue revealed the following: nearly circular particles measuring approximately 100 nm in diameter, with a concentric tri-lamellar shell-like structure, and containing an eccentric nucleoid structure, in or facing the lumen of adenocarcinoma tissue. Budding of these particles from the tumor cell membrane was also observed. Based on morphological characteristics, these particles were identified as B-type MMTV particles. Breast adenocarcinoma probably due to MMTV has also been observed in the mouse carcinogenicity study of abatacept (brand name, Orencia for I.V. Infusion 250 mg), and the increase in its incidence was attributed to extensive MMTV infection due to immunosuppression, a pharmacological effect of abatacept (according to the data submitted in the application for Orencia for I.V. Infusion 250 mg). Also in the high-dose topiroxostat groups, manifestations of MMTV infection might have been induced by immunodeficiency attributable to severe general physical deterioration, resulting in an increase in the incidence of breast adenocarcinoma. Furthermore, given that XOR inhibition has been suggested to have possible positive effects on breast adenocarcinoma cells (*in vitro* and *in vivo* increases in cell number and transplanted tumor volume) (Fini MA, *et al*., *Mol Cancer Res.* 2011;9:1242-54), the tumor volume (at the time of dissection) in the mice that were found to have breast adenocarcinoma was investigated using the data from the mouse carcinogenicity study of topiroxostat. The results showed no difference in tumor volume between any treatment groups. Although XOR has been reported to be involved in normal mammary gland differentiation (Fini MA, *et al*., *Mol Cancer Res.* 2011;9:1242-54), repeated dose toxicity studies showed normal development of mammary gland tissue both in mice and rats, with no morphological findings suggestive of differential inhibition. It is thus unlikely that XOR inhibition by topiroxostat is involved in the increased incidence of breast adenocarcinoma. Based on the above, the increase in the incidence of breast adenocarcinoma observed in the high dose groups in the mouse carcinogenicity studies is considered to be unlikely due to the direct effect of topiroxostat.

The rat carcinogenicity study detected angiosarcoma confined to the renal papilla in the high dose group. This may be attributed to the damage and regeneration of vascular endothelial cells and induction of vascular endothelial growth factor (VEGF) due to hypoxia which could be accompanied by severe nephropathy due to long-term deposition of xanthine crystals. It has been reported that hypoxia is involved in the mechanism of the development of angiosarcoma in rodents (Cohen SM, *et al*., *Toxicol Sci.* 2009;111:4-18). When primary cultured cells of the renal papilla isolated from a F344 rat, the strain used in the carcinogenicity study, were incubated under a hypoxic condition, VEGF increased in the medium. All animals with angiosarcoma were considered to have had severe chronic nephropathy because most of them were moribund or dead and because xanthine crystals, extensive inflammatory cell infiltration over the entire kidney, dilatation and basophilic changes in the renal tubule and collecting duct, and interstitial fibril formation were detected histologically. In addition, the renal papilla, where angiosarcoma occurred, provided evidence of tissue damage such as thrombus formation, pigmentation, and vasodilation in addition to hemorrhage. Taking into account the fact that precipitated crystals in urine are prone to accumulate in the papillary collecting duct, it was inferred that the overaccumulation directly caused the damage to the collecting duct and the surrounding tissues and that, in the carcinogenicity study, a long period of physical/mechanical stimulation of areas from the renal papilla to the renal pelvis by xanthine crystals resulted in sustained tissue damage, which led to the damage and regeneration of the capillary endothelium as well as tissue organization. Moreover, it was inferred that decreased papillary blood flow (Zimmerhackl BL, *et al*., *Kidney Int.* 1987;31:641-7) coupled with oxygen deficiency and anemia associated with nephropathy resulted in further persistence of hypoxia. Based on the above, it was concluded that the renal papillary angiosarcoma detected in the high dose group in the rat carcinogenicity study is unlikely to be a consequence of the direct effect of topiroxostat.

In addition, an increase in thyroid follicular cell adenoma was observed in the male high dose group in the rat carcinogenesis study. This was attributed to the metabolic abnormalities of thyroid hormone due to chronic renal failure. Since a certain portion of thyroxine (T4), a thyroid hormone, is converted to triiodothyronine (T3), which has higher physiological activity than T4, by 5'-deiodinase present in the liver, kidney, and thyroid gland, it is evident that the kidney plays an important role in the homeostasis of thyroid hormone. Because all rats with follicular cell adenoma died or became moribund owing to chronic renal failure, it was considered that the decrease in T3 due to severe renal disorders evoked persistent stimulation by thyroid-stimulating hormone via the hypothalamic-pituitary-thyroid axis negative feedback system, leading to the development of proliferative lesions of thyroid follicular cells. The above results indicate that the thyroid follicular cell adenoma detected in the high dose group in the rat carcinogenicity study is unlikely to be a consequence of the direct effect of topiroxostat.

Taking the above into account, the tumor detected in the carcinogenicity study occurred secondarily to the serious nephropathy caused by topiroxostat. Therefore, the carcinogenic risk of topiroxostat should be low in humans.

4. Clinical data

4.(i) Summary of biopharmaceutic data and associated analytical methods

4.(i).A Summary of the submitted data

Three different tablet formulations were used in clinical development. The formulations used in the main clinical studies are listed in Table 7. The proposed commercial formulations are uncoated 20, 40, and 60 mg tablets (Formulation C), among which 20 and 60 mg tablets are the same tablets as used in the late phase II and subsequent clinical studies (hereinafter, "topiroxostat" refers to Formulation C, and other formulations are referred to as "topiroxostat [Formulation A]" or "topiroxostat [Formulation B]" unless otherwise noted). Although 40 mg tablets were not used in clinical studies, their bioequivalence with 20 and 60 mg tablets has been shown by dissolution testing in accordance with "Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms" (PMSB/ELD Notification No. 64 dated February 14, 2000, partially revised by PFSB/ELD Notification No. 1124004 dated November 24, 2006).

Table 7. Summary of formulations used in main clinical studies

Type of formulation	Content	Phase of development (Study number)
Film-coated tablet (Formulation A)	20 mg	Phase I studies (FYX-051-111, FYX-051-112)
Film-coated tablet (Formulation B)	10, 20, 30 mg	Phase II exploratory study (FYX-051-221)
	20, 30, 40 mg[a)]	Phase I study (FYX-051-123) Phase II exploratory study (FYX-051-222)
Uncoated tablet (Formulation C)	20, 40, 60, 80 mg	Phase I studies (FYX-051-124, FYX-051-135, FYX-051-139, FY0001, FY0002) Late phase II study (FYX-051-323) Phase III studies (FYX-051-332, FY1001, FY1002, FY1003)

a) Drug substance was manufactured by a method different from that for the 10, 20, and 30 mg tablets

Topiroxostat concentrations in human plasma and urine and concentrations of topiroxostat N-oxide and N_1- and N_2-glucronide conjugates in human plasma were quantified[26] by LC-MS/MS, with the lower limit of quantification being 0.1 ng/mL for topiroxostat in human plasma and urine and 1 ng/mL for topiroxostat N-oxide and N_1- and N_2-glucronide conjugates in human plasma (in Studies FYX-051-111 and FYX-051-112, plasma N_1- and N_2-glucronide conjugates were measured by the hydrolysis technique,[27] with the lower limit of quantification being 3 ng/mL). Human urine concentrations of topiroxostat N-oxide and N_1- and N_2-glucronide conjugates were quantified by LC-MS, with the lower limit of quantification being 0.1 μg/mL for topiroxostat N-oxide and 1 μg/mL for N_1- and N_2-glucronide conjugates (in Studies FYX-051-111 and FYX-051-112, urine N_1- and N_2-glucronide conjugates were measured by the hydrolysis technique, with the lower limit of quantification being 10 ng/mL). Human plasma and urine concentrations of uric acid, xanthine, and hypoxanthine were quantified by HPLC, with the lower limit of quantification being 0.1 and 2.5 mg/dL for uric acid in plasma and urine, respectively, and for xanthine and hypoxanthine, 0.01 mg/dL in plasma and 0.1 mg/dL in urine.

[26] The concentrations of topiroxostat metabolites (topiroxostat N-oxide and N_1- and N_2-glucronide conjugates) were converted to topiroxostat concentrations by multiplying measured concentrations by the molecular mass ratio of topiroxostat to the measured metabolite.

[27] The concentration of N_1- and N_2-glucronide conjugates was quantified in Studies FYX-051-111 and FYX-051-112 by calculating the difference between the LC-MS/MS measurement of unchanged topiroxostat after hydrolysis and the concentration of unchanged topiroxostat in the sample prior to hydrolysis.

The submitted biopharmaceutic evaluation data included the results of Study FYX-051-139 and other studies.[28] The results from the main studies are described below.

Study on pharmacokinetics of, and food effects on final formulation (5.3.1.1-1, Study FYX-051-139, [redacted] 20[redacted])

A two-period crossover study was conducted in healthy Japanese adult male subjects (target number of subjects, 12) to study the pharmacokinetics and safety of, and food effects on topiroxostat.

A single oral dose of 60 mg of topiroxostat was administered under fasting or fed (within 15 minutes after a meal) conditions in Treatment Period 1 and Treatment Period 2. The study design included a 1-week washout period between the two treatment periods.

All 12 treated subjects were included in the safety analysis set, and 11 subjects were included in the pharmacokinetic analysis set with the exception of 1 subject who discontinued the study because of consent withdrawal during Treatment Period 2.

The pharmacokinetic parameters of unchanged topiroxostat after administration of topiroxostat under fasting or fed conditions are shown in Table 8.

Table 8. Pharmacokinetic parameters of unchanged topiroxostat after administration of topiroxostat under fasting or fed conditions

Dosing condition	C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\text{-}inf}$ (ng•h/mL)	$T_{1/2}$ (h)	k_{el} (1/h)	MRT (h)	CL_{tot}/F (L/h)	V_d/F (L)
Fasting	579.3 ± 284.6	0.9 ± 0.5	793.5 ± 139.2	10.9 ± 9.7	0.10 ± 0.05	2.5 ± 1.3	77.6 ± 12.7	1212.4 ± 1094.5
Fed	375.8 ± 145.3	2.3 ± 0.8	838.8 ± 223.9	6.7 ± 3.0	0.13 ± 0.06	3.7 ± 1.0	75.7 ± 17.8	704.6 ± 308.4

Mean ± SD

C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration; $AUC_{0\text{-}inf}$, area under the plasma concentration-time curve extrapolated to time = infinity; $T_{1/2}$, elimination half-life; k_{el}, elimination rate constant; MRT, mean residence time; CL_{tot}/F, apparent total body clearance; V_d/F, apparent volume of distribution

The effect of food was shown as the following fed/fasting ratios of geometric means for C_{max} and $AUC_{0\text{-}inf}$ [two-sided 90% confidence interval (CI)]: 0.70 [0.52, 0.96] and 1.04 [0.91, 1.19], respectively.

The results of the safety evaluation showed no adverse events.

4.(i).B Outline of the review by PMDA

Food effect

Given the prolongation of T_{max} and an approximately 30% decrease in C_{max} observed after a meal (fed conditions) in the study on pharmacokinetics of, and food effects on the final formulation of

[28] Bioequivalence has been demonstrated by the other submitted evaluation data, including: the data of the dissolution tests (5.3.1.4-1, 5.3.1.4-2, 5.3.1.4-3) to study the equivalence of allopurinol tablets to the allopurinol capsules (prepared by encapsulating allopurinol tablets) used as the control drug in late phase II studies, to the allopurinol capsules used as the control drug in phase III studies, and to the allopurinol capsule used as the control drug in late phase II and phase III studies, respectively.

topiroxostat (Study FYX-051-139), PMDA asked the applicant to explain the effect of pharmacokinetic changes on efficacy.

The applicant responded as follows:
Topiroxostat is not considered to be a highly polar compound. Therefore, it is unlikely that the prolongation of T_{max} and the decrease in C_{max} after a meal can be attributed to malabsorption.[29] Rather, they are considered to be mainly due to delayed gastric emptying after a meal. On the other hand, little effect was observed on $AUC_{0\text{-}inf}$. In terms of the pharmacodynamics, the effect of food (high-fat diet and normal diet) on blood uric acid level was studied in a single dose study (Study FYX-051-111), which showed that there was no effect, such as a decrease in blood uric acid-lowering activity, under fed conditions compared with fasting conditions [see Table 11 in "4.(ii).A.(2).1) Phase I single dose study"]. The pharmacodynamic action of topiroxostat was not affected despite the decrease in C_{max} because the blood uric acid-lowering effect of topiroxostat correlates not only with C_{max} but also with AUC.[30] Given that the AUC of topiroxostat was unaffected by eating, its efficacy is unlikely to be affected by food. The blood uric acid level has been reported to change in response to circadian rhythm, fasting (starved state), eating, and the types of food taken.[31]

As described above, given the multiple factors involved in the evaluation of the effect of food on the blood uric acid level, the effect of timing of topiroxostat administration on the efficacy of topiroxostat is considered to be minor based on the results from the clinical studies in patients (Studies FYX-051-221, FYX-051-222, FYX-051-323, FY1001, FYX-051-332, FY1002, and FY1003), which analyzed variability in serum uric acid levels.

PMDA accepted the applicant's response.

4.(ii) Summary of clinical pharmacology studies

4.(ii).A Summary of the submitted data

The submitted evaluation data included the results of a phase I single-dose study (Study FYX-051-111), a phase I repeated dose study (Study FYX-051-112), pharmacokinetic and pharmacodynamic studies in patients with renal impairment, elderly men, and elderly women (Studies FYX-051-123, FYX-051-124, and FYX-051-135), a drug interaction study with warfarin (Study FY0001), and a QT/QTc evaluation study (Study FY0002). The results of foreign clinical studies (Studies FY-051-1-1, FY-051-1-2, and FYX-051-137) were submitted as reference data. In addition, the results of the studies using human biomaterials were also submitted. The results from the main studies are described below.

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29 Distribution coefficient, Log P, of topiroxostat is 1.78 (1-octanol/water)

30 Correlation coefficient (r) was 0.9815 between C_{max} and ΔEC_{max}, 0.9518 between C_{max} and $\Delta AUEC_{0\text{-}48\,h}$, 0.9610 between $AUC_{0\text{-}inf}$ and ΔEC_{max}, and 0.9361 between $AUC_{0\text{-}inf}$ and $\Delta AUEC_{0\text{-}48\,h}$.

31 Uematsu T, *et al*., *J Pharmacol Exp Ther*. 1994;270:453-9, Lloyd-Mostyn RH, *et al*., *Ann Rheum Dis*. 1970;29:553-5, Guideline Revision Committee of the Japanese Society of Gout and Nucleic Acid Metabolism, ed. *Guideline for the management of hyperuricaemia and gout: second edition*, 110-2 and 116-21

4.(ii).A.(1) Studies using human biomaterials (4.2.2.3-4; 4.2.2.3-6; 4.2.2.6-2 to 7; 4.2.2.3-5, reference data; 4.2.2.4-8, reference data)

The mean protein binding (ultrafiltration) of ^{14}C-topiroxostat in human plasma was >97.5%,[32] 98.8%, and 98.4% at 20, 200, and 2000 ng/mL, respectively. The mean protein binding of ^{14}C-topiroxostat to human serum albumin, α_1-acid protein, and γ-globulin (all at 0.1, 1, and 10 μg/mL) was 92.3% to 93.2%, 12.3% to 16.8%, and 34.7% to 40.4%, respectively.

The effect of topiroxostat on the protein binding of concomitant drugs (representative drugs that may be coadministered with topiroxostat) was studied. The percent plasma protein binding[33] in the presence of topiroxostat (0.25, 1, and 4 μg/mL) was >99.5% for benzbromarone (2 and 20 μg/mL), 97.1% to 100.4% for probenecid (60 and 600 μg/mL), 99.8% to 100.3% for loxoprofen sodium (5 and 50 μg/mL), 100.0% to 100.1% for indomethacin (3 and 30 μg/mL), >99.9% for celecoxib (0.7 and 7 μg/mL), and 99.8% to 100.1% for warfarin (8 and 80 μg/mL). The effect of concomitant drugs on the protein binding of topiroxostat in terms of the percent protein binding[33] in the presence of the above drugs (at the same concentrations) was 98.1% to 100.0% with benzbromarone, 99.5% to 101.6% with probenecid, 99.5% to 101.3% with loxoprofen sodium, 98.7% to 100.1% with indomethacin, 98.4% to 100.8% with celecoxib, and 97.5% to 100.9% with warfarin.

The distribution of ^{14}C-topiroxostat (20, 200, and 2000 ng/mL) in blood cells was 6.7% to 12.8%.

Uridine diphosphate glucuronosyltransferase (UGT) isoforms (UGT1A1, 1A3, 1A4, 1A6, 1A7, 1A8, 1A9, 1A10, 2B4, 2B7, 2B15, and 2B17) involved in the metabolism of ^{14}C-topiroxostat were investigated using human liver UGT-expressing microsomes. The results showed generation of N_1- and N_2-glucuronide conjugates, major metabolites of topiroxostat, mediated by UGT1A1, 1A7, and 1A9, with UGT1A9 being particularly active (K_m was 64.1 and 72.2 μmol/L, respectively).

Inhibition of cytochrome P450 (CYP) isoforms (CYP1A1/2, 2A6, 2B6, 2C8/9, 2C19, 2D6, 2E1, and 3A4) by topiroxostat and topiroxostat N-oxide was investigated, and topiroxostat was found to most strongly inhibit CYP2C8/9 with a Ki of 14.8 μmol/L, which was followed by CYP1A1/2, 3A4, and 2C19 with Ki values of 21.9, 41.6, and 54.9 μmol/L, respectively. The IC_{50} values of topiroxostat and topiroxostat N-oxide against CYP2A6, 2B6, 2D6, and 2E1 were >100 μmol/L. Inhibition of CYP2C9 by topiroxostat was investigated with S-warfarin as the substrate, and the Ki for S-warfarin was determined as 14.6 μmol/L, which was similar to the Ki for tolbutamide (14.8 μmol/L), a substrate of CYP2C9.

Inhibition of transport via various drug transporters (MDR1, BCRP, OAT1, OAT3, OCT2, OATP1B1, and OATP1B3) by topiroxostat, topiroxostat N-oxide, and N_1- and N_2-glucuronide conjugates was

[32] Binding could not be calculated at 20 ng/mL because protein binding in the filtrate was below the detection limit, but was calculated to be >97.5%, by substituting the filtrate radioactivity at 20 ng/mL, at which protein binding in the filtrate was below the detection limit, with the background level.

[33] Relative change in plasma protein binding = (plasma protein binding when topiroxostat is added/plasma protein binding when topiroxostat is not added) × 100

investigated, and topiroxostat was found to most strongly inhibit OAT3 with an IC_{50} of 1.05 μmol/L, which was followed by OAT1, BCRP, and OATP1B1 with IC_{50} values of 2.85, 13.7, and 41.7 μmol/L, respectively. The IC_{50} values of topiroxostat against MDR1, OCT2, and OATP1B3 were >50 μmol/L. topiroxostat N-oxide most strongly inhibited OAT3 with an IC_{50} of 0.626 μmol/L, and also inhibited OAT1 (IC_{50}, 7.69 μmol/L), but the IC_{50} values against other isoforms were >10 μmol/L. N_1- and N_2-glucuronide conjugates had IC_{50} values of >50 μmol/L against all isoforms of drug transporters.

4.(ii).A.(2) Studies in healthy adults

4.(ii).A.(2).1) Phase I single-dose study (5.3.3.1-1, Study FYX-051-111, [redacted] 20[redacted] to [redacted] 20[redacted])

A randomized, placebo-controlled, double-blind, parallel-group, comparative study was conducted using a group sequential dose-escalation design in healthy Japanese adult male subjects (target number of subjects, 45) to study the pharmacokinetics, pharmacodynamics, and safety after a single dose of topiroxostat (formulation A).

A single oral dose of placebo or 20, 40, 80, 120, or 180 mg of topiroxostat was administered under fasting conditions. After a 1-week washout period, the subjects treated with 40 or 80 mg of topiroxostat under fasting conditions were once again treated orally at the same previous dose under fed conditions (40 mg, high fat diet; 80 mg, normal diet). At each dose level, 6 and 3 subjects were randomly assigned to the topiroxostat and placebo groups, respectively.

All 45 treated subjects were included in the pharmacokinetic, pharmacodynamic, and safety analysis sets.

The pharmacokinetic parameters of unchanged topiroxostat after a single oral dose of topiroxostat (Formulation A) are shown in Table 9.

Table 9. Pharmacokinetic parameters of unchanged topiroxostat after a single oral dose of topiroxostat (formulation A)

Dose	Dosing condition	C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\text{-inf}}$ (ng•h/mL)	$T_{1/2}$ (h)	CL_{tot}/F (L/h)	$Fe_{0\text{-48 h}}$ (%)	CL_R (mL/h)
20 mg	Fasting	229.9 ± 81.6	0.67 ± 0.41	225.4 ± 22.5	5.0 ± 1.8	89.5 ± 9.4	0.019 ± 0.004	17.4 ± 3.7
40 mg	Fasting	469.4 ± 246.8	0.83 ± 0.26	580.2 ± 109.4	7.5 ± 3.6	71.0 ± 13.5	0.025 ± 0.004	18.0 ± 5.7
	Fed	288.7 ± 120.6	1.08 ± 0.58	499.1 ± 111.2	5.2 ± 1.4	83.8 ± 19.7	0.026 ± 0.011	21.4 ± 7.4
80 mg	Fasting	822.3 ± 390.5	0.75 ± 0.27	1206.6 ± 257.5	5.2 ± 1.0	69.5 ± 18.3	0.020 ± 0.007	13.4 ± 3.0
	Fed	755.2 ± 225.6	0.92 ± 0.38	1278.6 ± 275.1	5.1 ± 1.1	65.1 ± 14.3	0.024 ± 0.008	15.2 ± 3.9
120 mg	Fasting	1318.4 ± 371.2	0.92 ± 0.49	2366.7 ± 666.7	4.6 ± 0.7	54.6 ± 17.5	0.031 ± 0.014	15.2 ± 3.6
180 mg	Fasting	1773.5 ± 926.6	0.75 ± 0.42	2838.2 ± 891.9	7.1 ± 5.0	68.9 ± 21.0	0.025 ± 0.012	15.5 ± 5.6

Mean ± SD, n = 6

C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration; $AUC_{0\text{-inf}}$, area under the plasma concentration-time curve extrapolated to time = infinity; $T_{1/2}$, elimination half-life; CL_{tot}/F, apparent total body clearance; $Fe_{0\text{-48 h}}$, urinary excretion rate during the 48 hours post-dose; CL_R, renal clearance

The pharmacokinetic parameters of metabolites after a single oral dose of topiroxostat (Formulation A) are shown in Table 10.

Table 10. Pharmacokinetic parameters of metabolites[a)] after a single oral dose of topiroxostat (Formulation A)

Metabolite	Dose	Dosing Condition	C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\text{-inf}}$ (ng•h/mL)	$T_{1/2}$ (h)	$Fe_{0\text{-48 h}}$ (%)
Glucuronide conjugates[b)]	20 mg	Fasting	185.1 ± 43.2	1.17 ± 0.26	503.9 ± 67.2	3.4 ± 2.5	52.3 ± 4.3
	40 mg	Fasting	291.9 ± 36.8	1.58 ± 0.38	971.6 ± 138.8	7.0 ± 2.7	55.9 ± 8.9
		Fed	216.6 ± 42.7	1.92 ± 1.07	762.2 ± 143.7	5.7 ± 3.1	55.3 ± 5.5
	80 mg	Fasting	586.1 ± 124.7	1.42 ± 0.20	1964.4 ± 295.0	7.4 ± 2.1	56.4 ± 4.0
		Fed	543.2 ± 123.1	1.58 ± 0.38	1854.3 ± 391.5	7.6 ± 4.8	52.4 ± 10.3
	120 mg	Fasting	1061.3 ± 200.6	1.33 ± 0.26	3492.7 ± 470.6	4.4 ± 1.2	59.9 ± 4.1
	180 mg	Fasting	1324.4 ± 334.1	1.25 ± 0.27	4932.3 ± 854.6	11.4 ± 7.5	59.6 ± 7.9
Topiroxostat N-oxide	20 mg	Fasting	29.3 ± 6.2	1.00 ± 0.32	71.6 ± 25.0	3.6 ± 1.6	4.9 ± 1.5
	40 mg	Fasting	48.7 ± 16.9	1.00 ± 0.00	151.3 ± 55.2	8.4 ± 4.8	4.6 ± 1.4
		Fed	40.0 ± 20.5	1.67 ± 1.17	130.9 ± 49.4	5.9 ± 3.9	10.2 ± 2.6
	80 mg	Fasting	50.3 ± 17.3	1.08 ± 0.20	192.3 ± 62.8	10.7 ± 4.9	5.3 ± 1.2
		Fed	48.3 ± 14.6	1.25 ± 0.42	171.8 ± 60.1	9.0 ± 5.3	5.2 ± 1.4
	120 mg	Fasting	63.0 ± 14.1	1.42 ± 0.20	306.4 ± 88.3	6.1 ± 2.3	5.0 ± 1.0
	180 mg	Fasting	59.1 ± 13.5	1.08 ± 0.20	443.2 ± 136.5	17.8 ± 9.5	4.5 ± 1.4

Mean ± SD, n = 6

C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration; $AUC_{0\text{-inf}}$, area under the plasma concentration-time curve extrapolated to time = infinity; $T_{1/2}$, elimination half-life; $Fe_{0\text{-48 h}}$, urinary excretion rate during the 48 hours post-dose

a) Values converted to topiroxostat concentration (the concentration of glucuronide conjugate was calculated from the topiroxostat concentration after hydrolysis [see footnote 27], and the concentration of topiroxostat N-oxide was converted to topiroxostat concentration by multiplying by the molecular mass ratio of topiroxostat to this metabolite [see footnote 26]).

b) N_1- and N_2-glucronide conjugates were not distinguished because both conjugates were measured collectively.

The pharmacodynamic parameters after a single oral dose of topiroxostat (Formulation A) are shown in Table 11.

Table 11. Pharmacodynamic parameters after a single oral dose of topiroxostat (Formulation A)

Dose	Dosing condition	Uric acid				Xanthine		Hypoxanthine	
		ΔEC_{max} (mg/dL)	$\Delta AUEC_{0\text{-48 h}}$ (ng•h/mL)	CL_R (dL/h)	$Ae_{0\text{-24 h}}$ (mg)	CL_R (dL/h)	$Ae_{0\text{-24 h}}$ (mg)	CL_R (dL/h)	$Ae_{0\text{-24 h}}$ (mg)
Placebo	Fasting	-0.32 ± 0.21	14.9 ± 9.3	5.2 ± 1.4	634.5 ± 98.6	33.3 ± 9.1	8.8 ± 2.1	14.1 ± 12.2	10.6 ± 2.2
20 mg	Fasting	-0.56 ± 0.15	8.4 ± 7.9	4.0 ± 0.7	477.1 ± 69.7	32.4 ± 7.8	41.5 ± 5.9	14.2 ± 3.5	23.5 ± 3.6
40 mg	Fasting	-0.86 ± 0.28	-16.5 ± 7.2	4.9 ± 1.0	549.2 ± 98.7	42.5 ± 11.1	89.5 ± 28.2	18.8 ± 4.8	35.9 ± 7.2
	Fed	-0.89 ± 0.27	-25.9 ± 12.0	6.5 ± 1.1	566.1 ± 67.9	43.4 ± 10.9	72.0 ± 16.7	15.9 ± 4.1	21.7 ± 3.8
80 mg	Fasting	-0.94 ± 0.18	-31.1 ± 9.6	4.8 ± 1.0	448.1 ± 94.0	42.8 ± 6.4	109.5 ± 21.0	23.9 ± 7.9	46.5 ± 11.1
	Fed	-1.12 ± 0.23	-36.4 ± 13.4	5.3 ± 0.8	508.1 ± 68.3	43.1 ± 5.3	91.0 ± 33.5	23.0 ± 6.9	28.9 ± 7.3
120 mg	Fasting	-1.17 ± 0.24	-39.2 ± 4.9	4.6 ± 0.5	493.9 ± 35.4	44.6 ± 7.5	147.0 ± 21.7	34.2 ± 7.0	56.3 ± 10.6
180 mg	Fasting	-1.52 ± 0.55	-54.5 ± 21.7	4.0 ± 0.6	426.5 ± 60.3	46.1 ± 11.7	150.8 ± 27.1	39.6 ± 8.4	63.5 ± 8.8

Mean ± SD, n = 6 (topiroxostat group), n = 15 (placebo group)

ΔEC_{max}, maximum change in plasma concentration from baseline; $\Delta AUEC_{0\text{-48 h}}$, change in area under the plasma concentration curve from baseline to 48 hours post-dose; CL_R, renal clearance; $Ae_{0\text{-24 h}}$, urinary excretion up to 24 hours post-dose

Safety results included the following 14 adverse events in 13 of 63 subjects: 1 event in 1 subject of the placebo group (β2 microglobulin urine increased), 2 events in 2 subjects of the topiroxostat 20 mg group (β2 microglobulin urine increased, white blood cell count increased), 1 event in 1 subject of the topiroxostat 40 mg group (β-N-acetyl-D-glucosaminidase [NAG] increased), 3 events in 3 subjects of the topiroxostat 80 mg group (β2 microglobulin urine increased), 4 events in 3 subjects of the topiroxostat 120 mg group (NAG increased in 2 subjects, diarrhoea/nausea), and 3 events in 3 subjects of the topiroxostat 180 mg group (diarrhoea, nausea, β2 microglobulin urine increased). The severity of all events was mild. Among them, adverse events for which a causal relationship to the study drug could not be ruled out (hereinafter, referred to as "adverse drug reactions") were diarrhoea/nausea" in the 120 mg group and "diarrhoea and nausea" in the 180 mg group. There were no deaths, serious adverse events, or adverse events leading to study discontinuation. There were no clinically relevant changes in vital signs, ECG, or physical findings.

4.(ii).A.(2).2) Phase I repeated dose study (5.3.3.1-2, Study FYX-051-112, [redacted] to [redacted] 20[redacted])

A randomized, placebo-controlled, double-blind, comparative study was conducted in healthy Japanese adult male subjects (target number of subjects, 26) to study the pharmacokinetics, pharmacodynamics, and safety during repeated administration of topiroxostat (Formulation A).

The placebo was orally administered in the placebo group after morning and evening meals for 7 days. In the topiroxostat group, subjects were treated for 7 days as follows: an 80 mg dose after the morning meal and the placebo after the evening meal in the 80 mg (in 1 dose) group[34]; a 40 mg dose after the morning and evening meals in the 80 mg (in 2 doses) group[35]; and an 80 mg dose after the morning and evening meals in the 160 mg (in 2 doses) group.[36] Six and 4 subjects were randomly assigned to the topiroxostat and placebo groups, respectively.[37]

All 26 treated subjects were included in the pharmacokinetic, pharmacodynamic, and safety analysis sets.

The pharmacokinetic parameters of unchanged topiroxostat during repeated oral administration of topiroxostat (Formulation A) are shown in Table 12.

Table 12. Pharmacokinetic parameters of unchanged topiroxostat during repeated oral administration of topiroxostat (Formulation A)

Daily dose	Day of measurement	C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\text{-}12\,h}$ (ng•h/mL)	$AUC_{0\text{-}24\,h}$ (ng•h/mL)	$T_{1/2}$ (h)	CL_{tot}/F (L/h)	$Fe_{0\text{-}24\,h}$ (%)
80 mg (in 1 dose)	Day 1	466.8 ± 194.9	1.08 ± 0.49	–	944.3 ± 362.1	6.9 ± 6.5	92.8 ± 29.7	0.024 ± 0.012
	Day 7	501.9 ± 224.4	1.33 ± 0.75	–	964.3 ± 364.3	6.9 ± 3.3	91.7 ± 31.3	0.025 ± 0.011
80 mg (in 2 doses)	Day 1	208.7 ± 79.6	1.17 ± 0.68	419.8 ± 94.7	–	4.3 ± 3.5	97.1 ± 25.5	0.020 ± 0.009
	Day 7	172.9 ± 42.2	1.42 ± 0.66	443.9 ± 86.8	–	6.2 ± 2.5	87.5 ± 17.0	0.013 ± 0.003
160 mg (in 2 doses)	Day 1	552.8 ± 233.3	1.17 ± 0.68	1044.4 ± 314.1	–	5.9 ± 6.8	75.2 ± 18.0	0.019 ± 0.008
	Day 7	608.5 ± 306.7	1.00 ± 0.55	1137.1 ± 267.2	–	8.0 ± 3.3	68.6 ± 14.7	0.013 ± 0.006

Mean ± SD; n = 6; –, not applicable

C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration, $AUC_{0\text{-}th}$, area under the plasma concentration-time curve up to time = t; $T_{1/2}$, elimination half-life; CL_{tot}/F, apparent total body clearance; $Fe_{0\text{-}24\,h}$, urinary excretion rate during the 24 hours post-dose

The trough concentration showed an almost identical time course in all topiroxostat groups on and after Day 2, and reached a steady state on Day 3 or 4.

The mean C_{max} and AUC[38] ratios of Day 7 to Day 1 (Day 7 level/Day 1 level) [two-sided 95% CI] were 1.14 [0.66, 1.62] and 1.03 [0.89, 1.16], respectively, in the 80 mg (in 1 dose) group, 0.92 [0.51, 1.33] and 1.09 [0.85, 1.32], respectively, in the 80 mg (in 2 doses) group, and 1.13 [0.79, 1.47] and 1.13 [0.89, 1.37], respectively, in the 160 mg (in 2 doses) group.

34 Four topiroxostat 20 mg tablets and 4 placebo tablets were administered after the morning and evening meals, respectively.

35 Two topiroxostat 20 mg tablets and 2 placebo tablets were administered after the morning and evening meals.

36 Four topiroxostat 20 mg tablets were administered after the morning and evening meals.

37 The 80 mg topiroxostat (in 1 dose) group and the 80 mg topiroxostat (in 2 doses) group were compared with a placebo group of 4 randomized subjects; the 160 mg topiroxostat (in 2 doses) group was compared with another placebo group of 4 randomized subjects.

38 $AUC_{0\text{-}24\,h}$ was used for the 80 mg (in 1 dose) group; $AUC_{0\text{-}12\,h}$ was used for the 80 mg (in 2 doses) group and the 160 mg (in 2 doses) group.

The pharmacokinetic parameters of metabolites during repeated oral administration of topiroxostat (Formulation A) are shown in Table 13.

Table 13. Pharmacokinetic parameters of metabolites[a)] during repeated oral administration of topiroxostat (Formulation A)

Metabolite	Daily dose[b)]	Day of measurement	C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\text{-}12\,h}$ (ng•h/mL)	$AUC_{0\text{-}24\,h}$ (ng•h/mL)	Fe (%)
Glucuronide conjugates[c)]	80 mg (in 2 doses)	Day 1	275.5 ± 72.1	1.83 ± 0.41	895.4 ± 160.2	–	50.0 ± 11.8
		Day 7	236.0 ± 63.9	2.33 ± 0.82	937.7 ± 180.2	1018.1 ± 203.2	57.0 ± 5.0
	160 mg (in 2 doses)	Day 1	528.7 ± 104.5	1.83 ± 0.41	1901.5 ± 212.7	-	57.0 ± 7.6
		Day 7	567.9 ± 170.5	1.83 ± 0.41	2119.2 ± 328.5	2318.3 ± 415.6	59.5 ± 5.1
Topiroxostat N-oxide	80 mg (in 2 doses)	Day 1	37.3 ± 7.4	1.67 ± 0.52	112.6 ± 32.8	–	7.2 ± 2.0
		Day 7	36.9 ± 7.9	1.67 ± 0.52	133.3 ± 22.0	149.9 ± 25.1	8.8 ± 1.5
	160 mg (in 2 doses)	Day 1	43.6 ± 13.3	1.33 ± 0.52	148.5 ± 54.7	–	5.0 ± 1.2
		Day 7	40.5 ± 14.1	1.50 ± 0.55	155.1 ± 61.5	181.2 ± 71.1	5.5 ± 1.2

Mean ± SD; n = 6; –, not applicable

C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration; $AUC_{0\text{-}th}$, area under the plasma concentration-time curve up to time = t; Fe, cumulative urinary excretion rate (excretion rate at Day 7 is the cumulative excretion rate during the 48 hours after the last dose)

a) Values converted to topiroxostat concentration (the concentration of glucuronide conjugate was calculated from the topiroxostat concentration after hydrolysis [see footnote 27], and the concentration of topiroxostat N-oxide was converted to topiroxostat concentration by multiplying by the molecular mass ratio of topiroxostat to this metabolite [see footnote 26]).

b) Metabolites in the 80 mg (in 1 dose) group were not measured.

c) N_1- and N_2-glucuronide conjugates were not distinguished because both conjugates were measured collectively.

The mean C_{max} and $AUC_{0\text{-}12\,h}$ ratios of Day 7 to Day 1 for glucuronide conjugates [two-sided 95% CI] were 0.87 [0.70, 1.03] and 1.05 [0.98, 1.11], respectively, in the 80 mg (in 2 doses) group and 1.08 [0.81, 1.35] and 1.11 [1.01, 1.22], respectively, in the 160 mg (in 2 doses) group. The mean C_{max} and $AUC_{0\text{-}12\,h}$ ratios of Day 7 to Day 1 for topiroxostat N-oxide [two-sided 95% CI] were 0.99 [0.92, 1.05] and 1.22 [1.04, 1.41], respectively, in the 80 mg (in 2 doses) group and 0.95 [0.65, 1.25] and 1.05 [0.77, 1.33], respectively, in the 160 mg (in 2 doses) group.

The pharmacodynamic parameters during repeated oral administration of topiroxostat (Formulation A) are shown in Table 14.

Table 14. Pharmacodynamic parameters during repeated oral administration of topiroxostat (Formulation A)

Daily dose	Day of measurement	Uric acid				Xanthine		Hypoxanthine	
		$\Delta EC_{24\,h}$ (mg/dL)	$AUEC_{0\text{-}24\,h}$ (mg•h/dL)	CL_R (dL/h)	$Ae_{0\text{-}24\,h}$ (mg)	CL_R (dL/h)	$Ae_{0\text{-}24\,h}$ (mg)	CL_R (dL/h)	$Ae_{0\text{-}24\,h}$ (mg)
Placebo	Day 1	-0.02 ± 0.11	127.4 ± 12.2	4.2 ± 0.7	536.2 ± 70.0	39.6 ± 12.4	7.8 ± 0.9	10.6 ± 3.3	8.0 ± 1.3
	Day 7	0.39 ± 0.36	135.3 ± 8.5	4.0 ± 0.8	540.2 ± 97.4	50.0 ± 15.4	8.1 ± 2.4	12.6 ± 4.3	9.1 ± 2.6
80 mg (in 1 dose)	Day 1	-0.60 ± 0.36	119.7 ± 10.7	3.8 ± 0.6	453.0 ± 66.8	46.4 ± 11.2	67.2 ± 20.9	27.1 ± 3.3	20.9 ± 2.3
	Day 7	-0.72 ± 0.67	106.3 ± 15.3	3.3 ± 0.5	354.0 ± 90.6	45.8 ± 8.6	75.9 ± 23.8	31.3 ± 7.9	25.1 ± 3.5
80 mg (in 2 doses)	Day 1	-1.12 ± 0.28	–	–	449.9 ± 93.0	–	80.9 ± 22.2	–	25.7 ± 4.7
	Day 7	-0.92 ± 0.42	–	–	350.3 ± 57.9	–	77.7 ± 8.4	–	24.4 ± 3.0
160 mg (in 2 doses)	Day 1	-1.54 ± 0.29	–	–	449.0 ± 78.2	–	109.1 ± 23.2	–	30.2 ± 4.9
	Day 7	-1.68 ± 0.53	–	–	303.2 ± 82.4	–	118.3 ± 30.6	–	42.7 ± 9.5

Mean ± SD; n = 6 (topiroxostat group); n = 8 (placebo group); –, not applicable

$\Delta EC_{24\,h}$, difference in plasma concentration from baseline to 24 hours post-dose; $AUEC_{0\text{-}24\,h}$, area under plasma concentration-time curve up to 24 hours post-dose; CL_R, renal clearance; $Ae_{0\text{-}24\,h}$, urinary excretion up to 24 hours post-dose

Safety results included the following 5 adverse events in 2 of 26 subjects: 2 events in 1 subject in the 80 mg (in 1 dose) group (aspartate aminotransferase [AST] increased/alanine aminotransferase [ALT] increased) and 3 events in 1 subject in the 160 mg (in 2 doses) group (feeling hot/β2 microglobulin urine increased/NAG increased). All events were classified as adverse drug reactions, but were mild. There were no deaths, serious adverse events, or adverse events leading to study discontinuation. There were no clinically relevant changes in vital signs, ECG, or physical findings.

4.(ii).A.(2).3) Human mass balance study (5.3.3.1-5: Study FYX-051-137, [redacted] to [redacted] 20[redacted], reference data)

An open-label study was conducted in healthy non-Japanese adult male subjects (target number of subjects, 6) to study the pharmacokinetics, metabolism, and excretion after administration of ^{14}C-topiroxostat.

A single oral dose of 80 mg of ^{14}C-topiroxostat was administered under fasting conditions.

All 6 treated subjects were included in the pharmacokinetic and safety analysis sets.

The pharmacokinetic parameters of radioactivity after a single oral dose of ^{14}C-labelled topiroxostat are shown in Table 15.

Table 15. Pharmacokinetic parameters of radioactivity after a single oral dose of ^{14}C-topiroxostat

Target entity	C_{max} (ng eq./mL)	T_{max} (h)	$AUC_{0\text{-inf}}$ (ng eq.•h/mL)	$T_{1/2}$ (h)
Total radioactivity (plasma)	1630 ± 502	0.54 ± 0.25	5087 ± 751	8.37 ± 4.06
Total radioactivity (blood)	997 ± 304	0.42 ± 0.13	3079 ± 642	12.1 ± 7.32
Unchanged topiroxostat (plasma)	1167	0.50	1645	1.59
N_1-glucuronide conjugate (plasma)	607	1.0	2173	2.67
N_2-glucuronide conjugate (plasma)	104	1.0	NC	NC
Topiroxostat N-oxide (plasma)	3.62	0.25	NC	NC
HP1 (unidentified metabolite) (plasma)	27.5	4.0	NC	NC

Total radioactivity, mean ± SD; values for unchanged topiroxostat and metabolites were calculated from the combined samples of 6 subjects; NC, not calculated; C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration; $AUC_{0\text{-inf}}$, area under the plasma concentration-time curve extrapolated to time = infinity; $T_{1/2}$, elimination half-life

After administration of a single dose of ^{14}C-topiroxostat, 101.6% (76.8% in urine, 24.8% in feces) of radioactivity was excreted up to 96 hours post-dose. There was no radioactivity in the expired air.

Safety results included 7 adverse events in 5 of 6 subjects (diarrhoea/flatulence in 2 subjects; vessel puncture site pain, rhinitis, and headache in 1 subject each), all of which were mild. Among these events, headache was classified as an adverse drug reaction. There were no deaths, serious adverse events, or adverse events leading to study discontinuation. There were no clinically relevant changes in vital signs, ECG, or physical findings.

4.(ii).A.(3) Intrinsic factors

4.(ii).A.(3).1) Pharmacokinetic and pharmacodynamic studies in subjects with renal impairment (5.3.3.3-1, Study FYX-051-123, [redacted] to [redacted] 20[redacted])

An open-label study was conducted in healthy Japanese adults and Japanese subjects with renal impairment[39] (target number of subjects, 18) to study the pharmacokinetics, pharmacodynamics, and safety of topiroxostat (formulation B) administration.

[39] Subjects were classified into normal subjects ($C_{in} \geq 90$ mL/min/1.73 m^2), those with mild renal impairment ($60 \leq C_{in} < 90$ mL/min/1.73 m^2), and those with moderate impairment ($30 \leq C_{in} < 60$ mL/min/1.73 m^2) based on inulin clearance.

A single oral dose of 80 mg of topiroxostat was administered under fasting conditions.

All 18 treated subjects were included in the safety analysis set, and 17 subjects were included in pharmacokinetic and pharmacodynamic analysis sets with the exception of 1 subject who had mild renal impairment and met the exclusion criteria.

The pharmacokinetic parameters of unchanged topiroxostat in healthy adults and subjects with renal impairment after a single oral dose of topiroxostat (Formulation B) are shown in Table 16.

Table 16. Pharmacokinetic parameters of unchanged topiroxostat in healthy adults and subjects with renal impairment after a single oral dose of topiroxostat (Formulation B)

	C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\text{-}inf}$ (ng•h/mL)	$T_{1/2}$ (h)	CL_{tot}/F (L/h)	$Fe_{0\text{-}24\ h}$ (%)	CL_R (mL/h)
Healthy adults	740.3 ± 411.1	0.67 ± 0.26	1161.5 ± 554.2	8.4 ± 2.9	85.1 ± 43.8	0.017 ± 0.008	12.8 ± 5.4
Subjects with mild renal impairment [a)]	806.7 ± 452.3	0.90 ± 0.65	1372.7 ± 659.3	6.7 ± 2.3	74.1 ± 43.0	0.022 ± 0.011	16.9 ± 14.0
Subjects with moderate renal impairment	713.2 ± 269.8	1.00 ± 0.55	1426.6 ± 622.4	7.2 ± 2.3	70.3 ± 42.7	0.031 ± 0.022	18.7 ± 10.1

Mean ± SD, n = 6

C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration; $AUC_{0\text{-}inf}$, area under the plasma concentration-time curve extrapolated to time = infinity; $T_{1/2}$, elimination half-life; CL_{tot}/F, apparent total body clearance; $Fe_{0\text{-}24\ h}$, urinary excretion rate up to 24 hours post-dose; CL_R, renal clearance

a) n = 5

The ratios of geometric mean C_{max} and $AUC_{0\text{-}inf}$ for topiroxostat of subjects with renal impairment to healthy subjects (subjects with renal impairment/healthy subjects) [two-sided 90% CI] were 0.89 [0.38, 2.11] and 1.17 [0.65, 2.11], respectively, in mild renal impairment and 0.99 [0.65, 1.51] and 1.23 [0.72, 2.11], respectively, in moderate renal impairment.

Metabolite pharmacokinetics revealed the following ratios of geometric mean C_{max} and $AUC_{0\text{-}inf}$ of subjects with renal impairment to healthy subjects [two-sided 90% CI]: for N_1-glucuronide conjugate, 1.51 [0.69, 3.28] and 1.40 [0.94, 2.09], respectively, in subjects with mild renal impairment and 1.73 [0.95, 3.17] and 1.70 [1.24, 2.33], respectively, in subjects with moderate renal impairment; for N_2-glucuronide conjugate, 1.62 [0.77, 3.42] and 1.52 [0.98, 2.36], respectively, in subjects with mild renal impairment and 1.79 [1.03, 3.12] and 1.67 [1.17, 2.39], respectively, in subjects with moderate renal impairment; and for the topiroxostat N-oxide, 1.07 [0.74, 1.55] and 0.99 [0.44, 2.21], respectively, in subjects with mild renal impairment and 1.13 [0.77, 1.65] and 1.18 [0.63, 2.20], respectively, in subjects with moderate renal impairment. The urinary excretion rates up to 24 hours post-dose ($Fe_{0\text{-}24\ h}$, mean ± SD) in healthy subjects, subjects with mild renal impairment, and subjects with moderate renal impairment were 34.7% ± 4.3%, 39.6% ± 3.7%, and 36.1% ± 3.7%, respectively, for N_1-glucuronide conjugate, 15.2% ± 3.0%, 18.3% ± 2.9%, and 16.1% ± 1.8%, respectively, for N_2-glucuronide conjugate, and 4.6% ± 2.2%, 4.4% ± 2.2%, and 3.6% ± 1.4%, respectively, for topiroxostat N-oxide.

The pharmacodynamic parameters in healthy adults and subjects with renal impairment after a single oral dose of topiroxostat (Formulation B) are shown in Table 17.

Table 17. Pharmacodynamic parameters in healthy adults and subjects with renal impairment after a single oral dose of topiroxostat (Formulation B)

	Uric acid					Xanthine		Hypoxanthine	
	ΔEC_{max} (mg/dL)	$\Delta AUEC_{0\text{-}24\ h}$ (mg•h/mL)	CL_R (dL/h)	$Ae_{\text{-}24\ h\text{-}0}$ (mg)	$Ae_{0\text{-}24h}$ (mg)	$Ae_{\text{-}24\ h\text{-}0}$ (mg)	$Ae_{0\text{-}24\ h}$ (mg)	$Ae_{\text{-}24\ h\text{-}0}$ (mg)	$Ae_{0\text{-}24\ h}$ (mg)
Healthy adults	-1.0 ± 0.1	-17.6 ± 3.0	3.9 ± 1.0	745.2 ± 93.9	499.4 ± 50.8	11.4 ± 4.0	97.8 ± 38.9	9.7 ± 3.8	39.8 ± 13.2
Subjects with mild renal impairment[a)]	-1.1 ± 0.4	-17.9 ± 8.4	4.1 ± 1.2	772.4 ± 148.5	443.5 ± 69.4	10.1 ± 2.2	91.1 ± 32.3	6.8 ± 2.5	30.6 ± 11.0
Subjects with moderate renal impairment	-1.2 ± 0.3	-19.4 ± 7.8	3.0 ± 0.5	633.9 ± 104.9	442.8 ± 70.3	10.4 ± 4.02	91.2 ± 16.9	5.6 ± 2.0	28.6 ± 6.3

Mean ± SD, n = 6

ΔEC_{max}, maximum change in plasma concentration from baseline; $\Delta AUEC_{0\text{-}24\ h}$, change in area under the plasma concentration curve from baseline to 24 hours post-dose; CL_R, renal clearance; $Ae_{\text{-}24\ h\text{-}0}$, urinary excretion up to 24 hours prior to administration; $Ae_{0\text{-}24\ h}$, urinary excretion up to 24 hours post-dose

a) n = 5

Safety results included the following 8 adverse events in 4 of 18 subjects: 1 event in 1 healthy subject (somnolence), 5 events in 1 subject with mild renal impairment (abdominal distension/nausea/vomiting/musculoskeletal stiffness/headache), and 2 events in 2 subjects with moderate renal impairment (arthralgia, hot flush). The severity of "nausea/vomiting" that occurred in a subject with mild renal impairment was moderate, but other events were mild. "Somnolence" in a healthy subject and "nausea/vomiting" in a subject with mild renal impairment were classified as adverse drug reactions. There were no deaths, serious adverse events, or adverse events leading to study discontinuation. There were no clinically relevant changes of concern in vital signs, ECG, or physical findings.

4.(ii).A.(3).2) Pharmacokinetic and pharmacodynamic study in elderly male subjects (5.3.3.3-2, Study FYX-051-124, [redacted] to [redacted] 20[redacted])

An open-label study was conducted in elderly and non-elderly Japanese male subjects[40] (target number of subjects, 12) to study the pharmacokinetics, pharmacodynamics, and safety of topiroxostat.

A single oral dose of 80 mg of topiroxostat was administered under fasting conditions.

All 12 treated subjects were included in the pharmacokinetic, pharmacodynamic, and safety analysis sets.

The pharmacokinetic parameters of unchanged topiroxostat after administration of a single oral dose of topiroxostat in elderly and non-elderly male subjects are shown in Table 18.

Table 18. Pharmacokinetic parameters of unchanged topiroxostat after administration of a single oral dose of topiroxostat in elderly and non-elderly male subjects

	C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\text{-}inf}$ (ng•h/mL)	$T_{1/2}$ (h)	CL_{tot}/F (L/h)	$Fe_{0\text{-}24\ h}$ (%)	CL_R (mL/h)
Non-elderly male subjects	969.1 ± 320.3	0.58 ± 0.20	1264.0 ± 190.7	7.3 ± 2.5	64.8 ± 12.4	0.010 ± 0.006	6.6 ± 3.1
Elderly male subjects	741.1 ± 570.6	0.92 ± 0.58	1213.8 ± 431.0	6.9 ± 0.6	70.8 ± 16.8	0.019 ± 0.017	11.8 ± 7.2

Mean ± SD, n = 6

C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration; $AUC_{0\text{-}inf}$, area under the plasma concentration-time curve extrapolated to time = infinity; $T_{1/2}$, elimination half-life; CL_{tot}/F, apparent total body clearance; $Fe_{0\text{-}24\ h}$, urinary excretion rate up to

[40] Elderly male subjects were defined as ≥65 years, and non-elderly male subjects were defined as ≥20 years and ≤35 years.

24 hours post-dose; CL_R, renal clearance

The ratios of geometric mean C_{max} and $AUC_{0\text{-}inf}$ for topiroxostat of elderly male subjects to non-elderly male subjects (elderly/non-elderly) [two-sided 90% CI] were 0.65 [0.37, 1.15] and 0.93 [0.73, 1.20], respectively.

Metabolite pharmacokinetics revealed the following ratios of geometric mean C_{max} and $AUC_{0\text{-}inf}$ of elderly male subjects to non-elderly male subjects [two-sided 90% CI]: 1.06 [0.71, 1.56] and 1.54 [1.19, 1.99], respectively, for N_1-glucuronide conjugate; 1.13 [0.74, 1.74] and 1.64 [1.24, 2.17], respectively, for N_2-glucuronide conjugate; and 0.75 [0.51, 1.10] and 0.91 [0.65, 1.28], respectively, for topiroxostat N-oxide.

The pharmacological parameters after administration of a single oral dose of the drug product in elderly and non-elderly male subjects are shown in Table 19.

Table 19. Pharmacological parameters after administration of a single oral dose of the drug product in elderly and non-elderly male subjects

	Uric acid					Xanthine		Hypoxanthine	
	ΔEC_{max} (mg/dL)	$\Delta AUEC_{0\text{-}24\ h}$ (mg•h/dL)	CL_R (dL/h)	$Ae_{\text{-}24\ h\text{-}0}$ (mg)	$Ae_{0\text{-}24\ h}$ (mg)	$Ae_{\text{-}24\ h\text{-}0}$ (mg)	$Ae_{0\text{-}24\ h}$ (mg)	$Ae_{\text{-}24\ h\text{-}0}$ (mg)	$Ae_{0\text{-}24\ h}$ (mg)
Non-elderly male subjects	-0.78 ± 0.33	-11.9 ± 5.8	3.6 ± 0.7	617.3 ± 124.6	398.7 ± 77.6	9.5 ± 1.3	98.3 ± 11.5	9.5 ± 2.9	43.7 ± 6.7
Elderly male subjects	-1.03 ± 0.19	-19.0 ± 3.4	4.0 ± 0.4	632.6 ± 80.7	398.8 ± 56.0	11.4 ± 2.1	116.3 ± 22.7	8.5 ± 3.5	34.5 ± 13.2

Mean ± SD, n = 6

ΔEC_{max}, maximum change in plasma concentration from baseline; $\Delta AUEC_{0\text{-}24\ h}$, change in area under the plasma concentration curve from baseline to 24 hours post-dose; CL_R, renal clearance; $Ae_{\text{-}24\ h\text{-}0}$, urinary excretion up to 24 hours prior to administration; $Ae_{0\text{-}24\ h}$, urinary excretion up to 24 hours post-dose

The results of the safety evaluation showed no adverse events.

4.(ii).A.(3).3) Pharmacokinetic and pharmacodynamic study in elderly female subjects (5.3.3.3-3, Study FYX-051-135, [redacted] to [redacted] 20[redacted])

An open-label study was conducted in elderly Japanese female subjects[41] (target number of subjects, 6) to study the pharmacokinetics, pharmacodynamics, and safety of the drug product.

A single oral dose of 80 mg of topiroxostat was administered under fasting conditions.

All 6 treated subjects were included in the pharmacokinetic, pharmacodynamic, and safety analysis sets.

The pharmacokinetic parameters of unchanged topiroxostat after administration of a single oral dose of the drug product in elderly female subjects are shown in Table 20.

[41] Defined as ≥65 years.

Table 20. Pharmacokinetic parameters of unchanged topiroxostat after administration of a single oral dose in elderly female subjects

	C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\text{-}inf}$ (ng•h/mL)	$T_{1/2}$ (h)	CL_{tot}/F (L/h)	$Fe_{0\text{-}24\ h}$ (%)	CL_R (mL/h)
Elderly female subjects	719.0 ± 468.8	0.67 ± 0.26	1523.5 ± 423.3	8.2 ± 4.9	55.4 ± 12.8	0.038 ± 0.024	19.3 ± 5.7

Mean ± SD, n = 6

C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration; $AUC_{0\text{-}inf}$, area under the plasma concentration-time curve extrapolated to time = infinity; $T_{1/2}$, elimination half-life; CL_{tot}/F, apparent total body clearance; $Fe_{0\text{-}24\ h}$, urinary excretion rate up to 24 hours post-dose; CL_R, renal clearance

The pharmacological parameters after administration of a single oral dose of the drug product in elderly female subjects are shown in Table 21.

Table 21. Pharmacological parameters after administration of a single oral dose of topiroxostat in elderly female subjects

	Uric acid					Xanthine		Hypoxanthine	
	ΔEC_{max} (mg/dL)	$\Delta AUEC_{0\text{-}24\ h}$ (mg•h/dL)	CL_R (dL/h)	$Ae_{\text{-}24\ h\text{-}0}$ (mg)	$Ae_{0\text{-}24\ h}$ (mg)	$Ae_{\text{-}24\ h\text{-}0}$ (mg)	$Ae_{0\text{-}24h}$ (mg)	$Ae_{\text{-}24\ h\text{-}0}$ (mg)	$Ae_{0\text{-}24\ h}$ (mg)
Elderly female subjects	-1.04 ± 0.20	-17.0 ± 4.0	5.2 ± 1.0	520.1 ± 62.2	348.6 ± 64.3	13.0 ± 1.4	142.1 ± 18.7	5.5 ± 1.3	28.0 ± 4.0

Mean ± SD, n = 6

ΔEC_{max}, maximum change in plasma concentration from baseline; $\Delta AUEC_{0\text{-}24\ h}$, change in area under the plasma concentration curve from baseline to 24 hours post-dose; CL_R, renal clearance; $Ae_{\text{-}24\ h\text{-}0}$, urinary excretion up to 24 hours prior to administration; $Ae_{0\text{-}24\ h}$, urinary excretion up to 24 hours post-dose

The results of the safety evaluation showed no adverse events.

4.(ii).A.(4) Drug interactions

Drug interaction study with warfarin (5.3.3.4-1, Study **FY0001, [redacted] to [redacted] 20[redacted])**

An open-label study was conducted in healthy Japanese adult male subjects (target number of subjects, 12) to study the pharmacokinetic and pharmacodynamic effects and safety of concomitant use of the drug product and warfarin.

A single oral dose of 5 mg of warfarin was administered under fasting conditions in the morning on Day 1 of Treatment Period 1 (single-agent warfarin period). Treatment Period 1 was followed by a washout period of ≥14 days, and subsequently by Treatment Period 2 (co-administration period), in which oral administration of 80 mg of topiroxostat was repeated twice daily after the morning and evening meals for 11 days, and a single oral dose of 5 mg of warfarin was administered under fasting conditions in the morning on Day 6 of Treatment Period 2.

All 12 treated subjects were included in the pharmacokinetic, pharmacodynamic, and safety analysis sets.

Pharmacokinetics revealed the following ratios of geometric mean C_{max} and $AUC_{0\text{-}144\ h}$ between co-administration and single-agent warfarin (co-administration/single-agent warfarin) [two-sided 90% CI]: 1.07 [0.92, 1.26] and 1.15 [1.04, 1.26], respectively, for R-warfarin; 1.11 [0.92, 1.33] and 1.47 [1.30, 1.67], respectively, for S-warfarin. The ratios of geometric mean C_{max} and $AUC_{0\text{-}144\ h}$ for topiroxostat between coadministration and single-agent topiroxostat (co-administration/single-agent

topiroxostat) [two-sided 90% CI] were 1.08 [0.75, 1.54] and 1.01 [0.80, 1.28], respectively.

Pharmacodynamics provided a co-administration/single-agent warfarin ratio of 1.04 [two-sided 90% CI: 0.99, 1.10] in geometric mean INR $AUC_{0\text{-}144\ h}$ calculated from the international normalized ratio for prothrombin time (PT-INR).

Safety results included 2 adverse events in 1 of 12 subjects (1 event each of ALT increased during the single-agent warfarin period and the co-administration period). Both events were classified as adverse drug reactions, but were mild. There were no deaths, serious adverse events, or adverse events leading to study discontinuation. There were no clinically relevant changes in vital signs, ECG, or physical findings.

4.(ii).A.(5) Pharmacodynamic study

QT/QTc evaluation study (5.3.4.1-1, Study FY0002, [redacted] to [redacted] 20[redacted])

A randomized, double-blind, placebo- and moxifloxacin-controlled, four-period, crossover study was conducted in healthy Japanese adults (target number of subjects, 48 [24 men and 24 women]) to investigate the effect of a single dose of the drug product on QT/QTc interval.

A single oral dose of placebo, 60 or 180 mg of topiroxostat, or 400 mg of moxifloxacin (positive control) was administered under fasting conditions. The study design included a washout period of ≥4 days between treatment periods.

All 48 treated subjects were included in the pharmacokinetic, pharmacodynamic, and safety analysis sets.

Pharmacokinetics of a single oral dose of 60 and 180 mg of topiroxostat showed C_{max} (mean ± SD) of 687 ± 432 and 1793 ± 1187 ng/mL, respectively, and T_{max} of 0.8 ± 0.5 and 1.1 ± 0.8 hours, respectively.

ECG showed that the least square means of baseline-adjusted, placebo-corrected QTcF interval[42] values (ΔΔQTcF) [two-sided 90% CI] after administration of 60 mg and 180 mg of topiroxostat reached maximum levels of 2.92 [0.59, 5.25] ms at 4 hours post-dose and 2.33 [-0.01, 4.67] ms at 1 hour post-dose, respectively, with the upper limit of CI below 10 ms. On the other hand, when moxifloxacin was administered, the least square mean of ΔΔQTcF [two-sided 90% CI] reached a maximum of 13.6 [11.2, 15.9] ms at 4 hours post-dose, and the lower limit of CI was above 5 ms at all time points between 1 and 24 hours post-dose.

Safety results included the following adverse events: 4 events in 4 of 47 subjects after administration of placebo (eye pruritus, constipation, chest pain, feeling hot), 5 events in 4 of 47 subjects after

[42] QT interval corrected using Fridericia's formula

administration of 60 mg of topiroxostat (nasopharyngitis, oropharyngeal pain, stomatitis/pain in extremity, dysmenorrhea), 2 events in 2 of 47 subjects after administration of 180 mg of topiroxostat (rhinitis, urinary incontinence), and 20 events in 12 of 48 subjects after administration of moxifloxacin (electrocardiogram QT prolonged [4 cases in 4 subjects], wound, hypersensitivity, nausea/headache, otitis media acute/ear pruritus/white blood cell count increased/differential white blood cell count abnormal, nausea, erythema/nasal congestion, nausea/arthralgia/ECG QT prolonged, AST increased/blood creatine phosphokinase increased). Among these events, those classified as adverse drug reactions included "feeling hot" after administration of placebo, "stomatitis" after administration of 60 mg of topiroxostat, and 10 events in 8 subjects after administration of moxifloxacin (4 events in 4 subjects of ECG QT prolonged; hypersensitivity, nausea/headache, nausea, nausea/ECG QT prolonged). The severity of "dysmenorrhea" after administration of 60 mg of topiroxostat and "otitis media acute/ear pruritus" and "hypersensitivity" after administration of moxifloxacin was moderate, while other events were mild. The study was discontinued in 1 subject during moxifloxacin treatment due to "otitis media acute." There were no deaths or serious adverse events. There were no clinically relevant changes in vital signs, ECG, or physical findings.

4.(ii).B Outline of the review by PMDA

4.(ii).B.(1) Pharmacokinetics and pharmacodynamics in patients with severe renal impairment

PMDA asked the applicant to explain the pharmacokinetics and pharmacodynamics in patients with severe renal impairment, taking into account the pharmacokinetics of topiroxostat in patients with renal impairment.

The applicant responded as follows:

Study FYX-051-123 on the pharmacokinetics of topiroxostat in patients with renal impairment showed that the urinary fractional excretion (Fe) of unchanged topiroxostat was <0.1%, and that topiroxostat was excreted as N_1- and N_2-glucuronide conjugates and topiroxostat N-oxide (approximate Fe: 35%-40%, 15%-18%, and 4%-5%, respectively). Therefore, the effect of decreased renal function on the plasma concentration of unchanged topiroxostat is considered to be minor. Study FYX-051-123 showed no noticeable differences in the renal clearance (CL_R) of unchanged topiroxostat between patients with mild or moderate renal impairment and healthy adults nor did it show any effect on the plasma concentration of unchanged topiroxostat. In addition, the pharmacokinetic parameters of major metabolites, i.e. N_1- and N_2-glucuronide conjugates and topiroxostat N-oxide (all of which are about ≥200 times less potent than unchanged topiroxostat in the inhibition of xanthine oxidoreductase [XOR]) did not differ significantly in comparison with healthy adults, and suggested that the pharmacokinetics of topiroxostat is unlikely to be susceptible to renal impairment. The pharmacodynamic results of Study FYX-051-123 (Table 17) showed neither marked potentiation nor attenuation of the serum uric acid-lowering effect in patients with mild or moderate renal impairment compared with healthy adults.

The plasma concentration of unchanged topiroxostat is therefore considered unlikely to increase in

patients with severe renal impairment. Meanwhile, the possibility cannot be ruled out that the plasma concentrations of metabolites, in particular N_1- and N_2-glucuronide conjugates and topiroxostat N-oxide, may increase when their renal clearance is reduced significantly. However, given that all of the XOR inhibitory activities of N_1- and N_2-glucuronide conjugates and topiroxostat N-oxide are about ≥200 times less potent than unchanged topiroxostat, the impact of any increase in the plasma concentrations of these metabolites on the serum uric acid-lowering effect is considered to be minor. Following 52 weeks of repeated oral administration of 300 mg/kg of topiroxostat to monkeys which have a metabolism similar to that of humans (4.2.2.4-6, 4.2.2.4-7), exposure ratios[43] for glucuronide conjugates (the total of N_1- and N_2-glucuronide conjugates) and topiroxostat N-oxide, in comparison with humans treated at the maximum recommended clinical dose,[7] were 17.7 and 1.45, respectively, in terms of C_{max} and 20.8 and 2.17, respectively, in terms of $AUC_{0\text{-}24\ h}$, but no safety problems were identified in this study.

Based on the above, any increases in the plasma metabolite concentrations are considered unlikely to affect the safety of patients with severe renal impairment. A caution statement: "Patients with severe renal impairment (safety has not been established because of insufficient clinical experience)" will be included in the "Careful Administration" subsection of the "PRECAUTIONS" section in the proposed package insert.

PMDA acknowledged the applicant's response from the pharmacokinetic and pharmacodynamic points of view, but will further discuss the efficacy and safety in patients with renal impairment in the clinical section [see "4.(iii).B.(6).1) Patients with renal impairment"].

4.(ii).B.(2) Pharmacokinetics in patients with hepatic impairment

PMDA asked the applicant to explain the pharmacokinetics in patients with hepatic impairment, taking into account the pharmacokinetic properties of the drug product.

The applicant responded as follows:

No clinical pharmacology study has been conducted in patients with hepatic impairment. Topiroxostat is mainly metabolized by glucuronidation, and it has been reported that even a decrease in liver function (such as metabolic activity and hepatic blood flow) due to hepatic impairment (cirrhosis) is unable to alter the activities of conjugating enzymes, and therefore unlikely to affect drugs metabolized by conjugation, including drugs with both high and low extraction ratios (Kato R, *Drug Metabology, second edition*, Tokyo Kagaku Dojin. 2000;132-5). Based on the above, even if patients with mild or moderate hepatic impairment are treated with topiroxostat, the plasma concentration of unchanged topiroxostat is unlikely to increase, and its impact on safety is minor.

On the other hand, given that the plasma concentration of unchanged topiroxostat, a drug subject to

[43] Exposure (minimum) in the 52-week repeated-dose toxicity studies in monkeys (4.2.2.4-6 or 4.2.2.4-7)/Exposure (maximum) at maximum recommended clinical dose (an 80 mg/dose twice daily)

metabolism in the liver, is expected to increase in patients with severe hepatic impairment who have extremely poor liver function, and that the safety of topiroxostat has not been established in patients with hepatic impairment because of insufficient clinical experience, a caution statement will be included in the "PRECAUTIONS" section of the proposed package insert by advising careful administration in patients with hepatic impairment irrespective of severity.

PMDA sees no major problem in advising careful administration in patients with hepatic impairment, but will further discuss the safety of the drug in patients with hepatic impairment in the clinical section [see "4.(iii).B.(6).2) Patients with hepatic impairment"].

4.(iii) Summary of clinical efficacy and safety

4.(iii).A Summary of the submitted data

The submitted evaluation data included the results of: a phase I single dose study (Study FYX-051-111) and a phase I repeated dose study (Study FYX-051-112) in healthy Japanese adult males; phase II exploratory studies (Studies FYX-051-221 and FYX-051-222), a late phase II study (Study FYX-051-323), a phase III study (Study FY1001), a 6-month treatment study (Study FYX-051-332), and a 58-week treatment study (Study FY1002) in patients; and a placebo-controlled study in patients with concurrent moderate renal impairment (Study FY1003).

4.(iii).A.(1) Clinical pharmacology studies

The results of a phase I single dose study (Study FYX-051-111) and a phase I repeated dose study (Study FYX-051-112) were used for the safety evaluation. For a summary of the studies and the safety data, see "4.(ii) Summary of clinical pharmacology studies."

4.(iii).A.(2) Phase II studies

4.(iii).A.(2).1) Phase II exploratory study (5.3.5.1-1, Study FYX-051-221, [redacted] to [redacted] 20[redacted])

A randomized, placebo-controlled, double-blind, parallel-group study was conducted in Japanese patients with hyperuricaemia including gout[44] (target number of subjects, 200) to evaluate the efficacy and safety of the drug product on an exploratory basis.

This study consisted of a run-in period (2 weeks) and a treatment period (initial phase, 2 weeks; maintenance phase, 6 weeks).

The placebo group received the placebo orally twice daily after the morning and evening meals throughout the treatment period. During the initial phase of treatment, the topiroxostat groups received topiroxostat orally twice daily after the morning and evening meals for 2 weeks at: 10 mg/dose (20

[44] Major inclusion criteria: Japanese patients with hyperuricaemia including gout; aged ≥20 and <65 years at the time of informed consent; serum uric acid level of ≥8.0 mg/dL at 2 or more time-points during the run-in period. A washout period of 14 days was provided before the run-in period for subjects who had taken drugs that affect the serum uric acid level (including drugs for gout and hyperuricaemia). Patients showing primary or secondary hyperuricaemia were excluded.

mg/day) in the topiroxostat 40 and 60 mg groups and 20 mg/dose (40 mg/day) in the topiroxostat 80 and 120 mg groups. During the maintenance phase, topiroxostat was orally administered twice daily after the morning and evening meals for 6 weeks at 20, 30, 40, and 60 mg/dose (a daily dose of 40, 60, 80, and 120 mg of topiroxostat, respectively) in the topiroxostat 40, 60, 80, and 120 mg groups, respectively.

All 186 treated subjects (36 in the placebo group, 38 in the topiroxostat 40 mg/day group, 37 in the topiroxostat 60 mg/day group, 38 in the topiroxostat 80 mg/day group, and 37 in the topiroxostat 120 mg/day group) were included in the safety analysis set and the full analysis set (FAS), and the FAS was defined as the efficacy analysis set. The study was discontinued in 7 subjects, including 1 subject (adverse events) in the placebo group, 2 subjects (protocol non-compliance and consent withdrawal, 1 subject each) in the topiroxostat 40 mg/day group, 1 subject (adverse events) in the topiroxostat 80 mg/day group, and 3 subjects (protocol non-compliance, 2 subjects; consent withdrawal, 1 subject) in the topiroxostat 120 mg/day group.

The efficacy in terms of the primary endpoint, i.e. percentage decrease in serum uric acid level from baseline at the end of treatment in the FAS, is shown in Table 22.

Table 22. Percentage decrease in serum uric acid level from baseline at the end of treatment (Study FYX-051-221, FAS)

	Placebo group (n = 36)	Topiroxostat 40 mg/day group (n = 38)	Topiroxostat 60 mg/day group (n = 37)	Topiroxostat 80 mg/day group (n = 38)	Topiroxostat 120 mg/day group (n = 37)
Serum uric acid level at baseline (mg/dL)	9.13 ± 0.94	9.27 ± 1.12	9.22 ± 1.04	9.25 ± 1.12	9.15 ± 0.98
Serum uric acid level at the end of treatment (mg/dL)[a)]	9.26 ± 1.15 (n = 35)	7.09 ± 1.08 (n = 36)	7.14 ± 1.20 (n = 37)	6.46 ± 1.35 (n = 37)	6.32 ± 1.29 (n = 35)
Percentage decrease in serum uric acid level from baseline at the end of treatment [a)] (%)	-1.62 ± 10.82 (n = 35)	23.52 ± 9.52 (n = 36)	22.43 ± 10.72 (n = 37)	30.03 ± 11.95 (n = 37)	30.77 ± 12.18 (n = 35)
Percentage decrease in serum uric acid level from baseline at the end of treatment [b)] (%) (LOCF)	-1.06 ± 11.18 (n = 36)	23.39 ± 9.42 (n = 37)	22.43 ± 10.72 (n = 37)	30.14 ± 11.81 (n = 38)	29.05 ± 14.08 (n = 37)

Mean ± SD

a) It was decided that, if the measurement at 8 weeks post-dose was missing, the measurement closer to the end of treatment would be chosen from the measurements at 4 and 6 weeks post-dose for the evaluation of the measurement at the end of treatment. Among subjects withdrawn from the study, 5 subjects with data only at 2 weeks post-dose (1 subject in the placebo group, 1 subject in the topiroxostat 40 mg/day group, 1 subject in the topiroxostat 80 mg/day group, and 2 subjects in the topiroxostat 120 mg/day group) and 1 subject without post-dose data (topiroxostat 40 mg/day group) were excluded from analysis.

b) The results of subjects excluded from analysis in a) were imputed by Last Observation Carried Forward (LOCF). However, 1 subject in the topiroxostat 40 mg group was excluded from analysis because post-dose data were missing. Results of post-hoc analysis.

The results for the secondary endpoint, i.e. time course of serum uric acid levels, are shown in Table 23.

Table 23. Time course of serum uric acid levels (FYX-051-221 study, FAS)

Time point of evaluation	Placebo group	Topiroxostat 40 mg/day group	Topiroxostat 60 mg/day group	Topiroxostat 80 mg/day group	Topiroxostat 120 mg/day group
Baseline	9.13 ± 0.94 (n = 36)	9.27 ± 1.12 (n = 38)	9.22 ± 1.04 (n = 37)	9.25 ± 1.12 (n = 38)	9.15 ± 0.98 (n = 37)
Week 2[a)]	9.10 ± 1.04 (n = 36)	7.55 ± 1.04 (n = 36)	7.76 ± 1.13 (n = 37)	7.45 ± 1.32 (n = 38)	7.24 ± 1.18 (n = 36)
Week 4	9.09 ± 1.07 (n = 35)	7.22 ± 1.35 (n = 36)	6.97 ± 1.11 (n = 37)	6.73 ± 1.24 (n = 37)	6.18 ± 1.25 (n = 35)
Week 6	9.05 ± 1.00 (n = 35)	7.06 ± 1.08 (n = 35)	6.75 ± 1.16 (n = 37)	6.47 ± 1.28 (n = 37)	6.17 ± 1.24 (n = 34)
Week 8	9.30 ± 1.13 (n = 34)	7.09 ± 1.08 (n = 36)	7.14 ± 1.20 (n = 37)	6.28 ± 1.14 (n = 33)	6.31 ± 1.31 (n = 34)
End of treatment	9.26 ± 1.15 (n = 35)	7.09 ± 1.08 (n = 36)	7.14 ± 1.20 (n = 37)	6.46 ± 1.35 (n = 37)	6.32 ± 1.29 (n = 35)

Unit, mg/dL; Mean ± SD

a) Values during the period when a 10 mg dose was administered twice daily (20 mg/day) in the topiroxostat 40 and 60 mg/day groups, and values during the period when a 20 mg dose was administered twice daily (40 mg/day) in the topiroxostat 80 and 120 mg/day groups.

The percentage of subjects who achieved the target serum uric acid level of ≤6.0 mg/dL at the end of treatment is shown in Table 24.

Table 24. Percentage of subjects achieving a serum uric acid level of ≤6.0 mg/dL at the end of treatement (Study FYX-051-221, FAS)

	Placebo group (n = 35)	Topiroxostat 40 mg/day group (n = 36)	Topiroxostat 60 mg/day group (n = 37)	Topiroxostat 80 mg/day group (n = 37)	Topiroxostat 120 mg/day group (n = 35)
Percentage of subjects achieving a serum uric acid level of ≤6.0 mg/dL (number of subjects achieving ≤6.0 mg/dL)	0.0 (0)	19.4 (7)	21.6 (8)	43.2 (16)	40.0 (14)
Two-sided 95% CI	[0.00, 10.00]	[8.19, 36.02]	[9.83, 38.21]	[27.10, 60.51]	[23.87, 57.89]

Safety results showed the following cumulative incidence of adverse events at the end of study drug administration: 75.0% (27 of 36 subjects) in the placebo group, 71.1% (27 of 38 subjects) in the topiroxostat 40 mg/day group, 75.7% (28 of 37 subjects) in the 60 topiroxostat mg/day group, 63.2% (24 of 38 subjects) in the topiroxostat 80 mg/day group, and 48.6% (18 of 37 subjects) in the topiroxostat 120 mg/day group. The incidence of adverse drug reactions was 30.6% (11 of 36 subjects) in the placebo group, 31.6% (12 of 38 subjects) in the topiroxostat 40 mg/day group, 32.4% (12 of 37 subjects) in the topiroxostat 60 mg/day group, 23.7% (9 of 38 subjects) in the topiroxostat 80 mg/day group, and 27.0% (10 of 37 subjects) in the topiroxostat 120 mg/day group. The adverse events and/or adverse drug reactions reported in ≥5% of subjects in any treatment group are shown in Table 25.

Table 25. Adverse events and/or adverse drug reactions reported in ≥5% of subjects in any treatment group (Study FYX-051-221, safety analysis set)

Name of event	Placebo group (n = 36)		Topiroxostat 40 mg/day group (n = 38)		Topiroxostat 60 mg/day group (n = 37)		Topiroxostat 80 mg/day group (n = 38)		Topiroxostat 120 mg/day group (n = 37)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
Any event	75.0 (27)	30.6 (11)	71.1 (27)	31.6 (12)	75.7 (28)	32.4 (12)	63.2 (24)	23.7 (9)	48.6 (18)	27.0 (10)
Stomatitis	5.6 (2)	0.0 (0)	0.0 (0)	0.0 (0)	2.7 (1)	2.7 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Nasopharyngitis	16.7 (6)	0.0 (0)	10.5 (4)	0.0 (0)	8.1 (3)	0.0 (0)	2.6 (1)	0.0 (0)	2.7 (1)	0.0 (0)
ALT increased	5.6 (2)	5.6 (2)	5.3 (2)	5.3 (2)	8.1 (3)	5.4 (2)	7.9 (3)	0.0 (0)	8.1 (3)	5.4 (2)
AST increased	0.0 (0)	0.0 (0)	7.9 (3)	7.9 (3)	5.4 (2)	5.4 (2)	5.3 (2)	0.0 (0)	5.4 (2)	2.7 (1)
β2 microglobulin urine increased	5.6 (2)	5.6 (2)	2.6 (1)	2.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	2.7 (1)	0.0 (0)
NAG increased	16.7 (6)	11.1 (4)	15.8 (6)	10.5 (4)	13.5 (5)	13.5 (5)	5.3 (2)	5.3 (2)	5.4 (2)	0.0 (0)
Blood bilirubin increased	0.0 (0)	0.0 (0)	5.3 (2)	2.6 (1)	2.7 (1)	0.0 (0)	2.6 (1)	2.6 (1)	5.4 (2)	0.0 (0)
Blood creatine phosphokinase increased	8.3 (3)	0.0 (0)	13.2 (5)	0.0 (0)	10.8 (4)	2.7 (1)	5.3 (2)	2.6 (1)	5.4 (2)	0.0 (0)
Blood triglycerides increased	2.8 (1)	0.0 (0)	2.6 (1)	0.0 (0)	2.7 (1)	0.0 (0)	7.9 (3)	0.0 (0)	5.4 (2)	0.0 (0)
γ-glutamyltransferase increased	0.0 (0)	0.0 (0)	5.3 (2)	5.3 (2)	8.1 (3)	0.0 (0)	2.6 (1)	2.6 (1)	0.0 (0)	0.0 (0)
Blood urine present	0.0 (0)	0.0 (0)	2.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	5.3 (2)	2.6 (1)	0.0 (0)	0.0 (0)
White blood cell count decreased	0.0 (0)	0.0 (0)	5.3 (2)	2.6 (1)	2.7 (1)	0.0 (0)	5.3 (2)	0.0 (0)	2.7 (1)	0.0 (0)
Platelet count increased	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	5.3 (2)	0.0 (0)	0.0 (0)	0.0 (0)
Arthralgia	5.6 (2)	0.0 (0)	0.0 (0)	0.0 (0)	5.4 (2)	2.7 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Gout arthritis[45]	5.6 (2)	5.6 (2)	2.6 (1)	2.6 (1)	2.7 (1)	2.7 (1)	13.2 (5)	13.2 (5)	16.2 (6)	16.2 (6)
Pain in extremity	8.3 (3)	2.8 (1)	0.0 (0)	0.0 (0)	2.7 (1)	0.0 (0)	2.6 (1)	2.6 (1)	2.7 (1)	2.7 (1)
Headache	0.0 (0)	0.0 (0)	5.3 (2)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)

% incidence (number of subjects with events), MedDRA/J (ver. 9.1)

[45] Although "gouty arthritis" is listed in the terminology of MedDRA, "gout arthritis" is used hereinafter.

Neither deaths nor serious adverse events occurred. The only adverse event leading to study discontinuation was "gout arthritis" (1 subject each in the placebo group and the topiroxostat 80 mg/day group), and both cases were classified as adverse drug reactions.

The cumulative incidence of gout arthritis at the end of study drug administration was 5.6% (2 of 36 subjects) in the placebo group, 2.6% (1 of 38 subjects) in the topiroxostat 40 mg/day group, 2.7% (1 of 37 subjects) in the topiroxostat 60 mg/day group, 13.2% (5 of 38 subjects) in the topiroxostat 80 mg/day group, and 16.2% (6 of 37 subjects) in the topiroxostat 120 mg/day group. The incidence of gout arthritis in each treatment period is shown in Table 26.

Table 26. Incidence of gout arthritis by treatment time point (Study FYX-051-221, safety analysis set)

Time point	Placebo group	Topiroxostat 40 mg/day group	Topiroxostat 60 mg/day group	Topiroxostat 80 mg/day group	Topiroxostat 120 mg/day group
Week 2[a)]	5.6 (2/36)	0.0 (0/38)	0.0 (0/37)	5.3 (2/38)	5.4 (2/37)
Week 4	0.0 (0/35)	2.7 (1/37)	2.7 (1/37)	2.7 (1/37)	2.8 (1/36)
Week 6	2.9 (1/35)	0.0 (0/36)	0.0 (0/37)	0.0 (0/37)	2.9 (1/35)
Week 8	0.0 (0/35)	0.0 (0/36)	0.0 (0/37)	5.4 (2/37)	5.7 (2/35)
Overall period	5.6 (2/36)	2.6 (1/38)	2.7 (1/37)	13.2 (5/38)	16.2 (6/37)

% incidence (number of subjects with events/number of analyzed subjects)

There were no clinically relevant changes in vital signs or 12-lead ECG.

4.(iii).A.(2).2) Phase II exploratory study (5.3.5.1-2, Study FYX-051-222, [redacted] to [redacted] 20[redacted])

A randomized, double-blind, parallel-group study was conducted in Japanese patients with hyperuricaemia including gout[46] (target number of subjects, 72) to evaluate the dose-response relationship and safety of the drug product.

This study consisted of a run-in period (1 to 4 weeks) and a treatment period (initial phase, 2 weeks; maintenance phase, 10 weeks).

During the initial phase, an oral dose of 20 mg of topiroxostat was administered twice daily (40 mg/day) for 2 weeks. During the maintenance phase, an oral dose of 40, 60, and 80 mg of topiroxostat was administered twice daily (a daily dose of 80, 120, and 160 mg of topiroxostat, respectively) in the topiroxostat 80, 120, and 160 mg groups, respectively, after the morning and evening meals for 10 weeks.[47]

All 74 treated subjects (24 in the topiroxostat 80 mg/day group, 25 in the topiroxostat 120 mg/day group, and 25 in the topiroxostat 160 mg/day group) were included in the safety analysis set and the FAS, and the FAS was defined as the efficacy analysis set. The study was discontinued in 5 subjects,

[46] Major inclusion criteria: Japanese patients with hyperuricaemia including gout; aged ≥20 and <65 years at the time of informed consent; serum uric acid level of ≥8.0 mg/dL in the run-in period. A 14-day washout period was provided before the run-in period in subjects who had taken drugs that affect serum uric acid level (including drugs for gout and hyperuricaemia). Patients showing primary or secondary hyperuricaemia were excluded.

[47] When gout arthritis occurred and did not disappear during the initial phase, the initial dose was allowed to be continued for up to 1 week. Nevertheless, it was decided that the overall treatment period (the initial period plus the maintenance period) should not exceed 13 weeks.

including 1 subject (adverse events) in the topiroxostat 80 mg/day group, 2 subjects (consent withdrawal and adverse events, 1 subject each) in the topiroxostat 120 mg/day group, and 2 subjects (consent withdrawal and adverse events, 1 subject each) in the topiroxostat 160 mg/day group.

The efficacy in terms of the primary endpoint, i.e. percentage decrease in serum uric acid level from baseline at the end of treatment in the FAS, is shown in Table 27. The Jonckheere-Terpstra test detected statistical significance ($P < 0.001$, a two-sided significance level of 5%) in all treatment groups (the topiroxostat 80, 120, and 160 mg/day groups).

Table 27. Percentage decrease in serum uric acid level from baseline at the end of study drug administration (Study FYX-051-222, FAS)

	Topiroxostat 80 mg/day group (n = 24)	Topiroxostat 120 mg/day group (n = 25)	Topiroxostat 160 mg/day group (n = 25)
Serum uric acid level at baseline (mg/dL)	9.69 ± 1.31 (n = 24)	9.53 ± 1.07 (n = 25)	9.66 ± 1.43 (n = 25)
Serum uric acid level at the end of study drug administration (mg/dL)	6.72 ± 1.14 (n = 23)	5.86 ± 1.13 (n = 23)	5.17 ± 1.36 (n = 23)
Percentage decrease in serum uric acid level from baseline at the end of treatment[a)] (%)	29.90 ± 8.35 (n = 23)	38.77 ± 8.74 (n = 23)	47.18 ± 8.33 (n = 23)
P-value[b)]	$P < 0.001$		
Percentage decrease in serum uric acid level from baseline at the end of treatment[c)] (%) (LOCF)	29.95 ± 8.17	36.32 ± 12.22	46.90 ± 8.26

Mean ± SD

a) It was decided that, when the measurement at 12 weeks post-dose was missing, the measurement at 8 weeks post-dose would be used for evaluation of the measurement at the end of treatment. Among subjects withdrawn from the study, 4 subjects with data only at 2 weeks post-dose (1 subject in the topiroxostat 80 mg/day group, 2 subjects in the topiroxostat 120 mg/day group, and 1 subject in the topiroxostat 160 mg/day group) and 1 subject without post-dose data (topiroxostat 160 mg group) were excluded from analysis.

b) Jonckheere-Terpstra test with a two-sided significance level of 5%

c) The results of subjects excluded from analysis in a) were imputed by LOCF. However, 1 subject in the topiroxostat 160 mg/day group was excluded from analysis because post-dose data were missing. Results of post-hoc analysis.

The results for the secondary endpoint, i.e. time course of serum uric acid levels, are shown in Table 28.

Table 28. Time course of serum uric acid levels (Study FYX-051-222, FAS)

Time point of evaluation	Topiroxostat 80 mg/day group	Topiroxostat 120 mg/day group	Topiroxostat 160 mg/day group
Baseline	9.69 ± 1.31 (n = 24)	9.53 ± 1.07 (n = 25)	9.66 ± 1.43 (n = 25)
Week 2[a)]	7.59 ± 1.15 (n = 24)	7.54 ± 1.33 (n = 25)	7.30 ± 1.18 (n = 24)
Week 4	6.60 ± 1.34 (n = 23)	5.99 ± 1.23 (n = 22)	5.43 ± 1.32 (n = 23)
Week 8	6.71 ± 1.09 (n = 21)	6.22 ± 1.09 (n = 23)	5.43 ± 1.42 (n = 22)
Week 12	6.72 ± 1.14 (n = 23)	5.83 ± 1.15 (n = 22)	5.16 ± 1.39 (n = 22)
End of treatment	6.72 ± 1.14 (n = 23)	5.86 ± 1.13 (n = 23)	5.17 ± 1.36 (n = 23)

Unit, mg/dL; Mean ± SD

a) Values during the period when a 20 mg dose was administered twice daily (40 mg/day) in all treatment groups.

The percentage of subjects who achieved the target serum uric acid level of ≤6.0 mg/dL at the end of treatment is shown in Table 29.

Table 29. Percentage of subjects achieving a serum uric acid level of ≤6.0 mg/dL at the end of treatment (Study FYX-051-222, FAS)

	Topiroxostat 80 mg/day group (n = 23)	Topiroxostat 120 mg/day group (n = 23)	Topiroxostat 160 mg/day group (n = 23)
Percentage of subjects achieving a serum uric acid level of ≤6.0 mg/dL (number of subjects achieving ≤6.0 mg/dL)	26.1 (6)	60.9 (14)	73.9 (17)
Two-sided 95% CI	[10.2, 48.4]	[38.5, 80.3]	[51.6, 89.8]

Safety results showed the following cumulative incidence of adverse events at the end of treatment: 70.8% (17 of 24 subjects) in the topiroxostat 80 mg/day group, 72.0% (18 of 25 subjects) in the topiroxostat 120 mg/day group, and 80.0% (20 of 25 subjects) in the topiroxostat 160 mg/day group. The incidence of adverse drug reactions was 37.5% (9 of 24 subjects) in the topiroxostat 80 mg/day group, 32.0% (8 of 25 subjects) in the topiroxostat 120 mg/day group, and 40.0% (10 of 25 subjects) in the topiroxostat 160 mg/day group. The adverse events and/or adverse drug reactions reported in ≥5% of subjects in any treatment group are shown in Table 30.

Table 30. Adverse events and/or adverse drug reactions reported in ≥5% of subjects in any treatment group (Study FYX-051-222, safety analysis set)

Name of event	Topiroxostat 80 mg/day group (n = 24)		Topiroxostat 120 mg/day group (n = 25)		Topiroxostat 160 mg/day group (n = 25)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
Any event	70.8 (17)	37.5 (9)	72.0 (18)	32.0 (8)	80.0 (20)	40.0 (10)
Nasopharyngitis	20.8 (5)	0.0 (0)	32.0 (8)	0.0 (0)	28.0 (7)	0.0 (0)
ALT increased	20.8 (5)	16.7 (4)	8.0 (2)	0.0 (0)	8.0 (2)	4.0 (1)
AST increased	12.5 (3)	8.3 (2)	4.0 (1)	0.0 (0)	16.0 (4)	4.0 (1)
β2 microglobulin increased	4.2 (1)	0 (0.0)	8.0 (2)	0.0 (0)	0.0 (0)	0.0 (0)
β2 microglobulin urine increased	4.2 (1)	0 (0.0)	8.0 (2)	0.0 (0)	8.0 (2)	0.0 (0)
NAG increased	8.3 (2)	8.3 (2)	12.0 (3)	4.0 (1)	16.0 (4)	12.0 (3)
Blood creatine phosphokinase increased	12.5 (3)	0.0 (0)	12.0 (3)	0.0 (0)	4.0 (1)	0.0 (0)
Blood triglycerides increased	8.3 (2)	0.0 (0)	12.0 (3)	0.0 (0)	0.0 (0)	0.0 (0)
γ-glutamyltransferase increased	16.7 (4)	12.5 (3)	4.0 (1)	0.0 (0)	4.0 (1)	0.0 (0)
Gout arthritis	16.7 (4)	16.7 (4)	12.0 (3)	12.0 (3)	20.0 (5)	20.0 (5)
Pain in extremity	8.3 (2)	4.2 (1)	4.0 (1)	4.0 (1)	0.0 (0)	0.0 (0)
Limb discomfort	0.0 (0)	0.0 (0)	8.0 (2)	8.0 (2)	0.0 (0)	0.0 (0)

% incidence (number of subjects with events), MedDRA/J (ver. 11.0)

No deaths occurred. The only serious adverse event was “cholelithiasis” (1 subject) in the topiroxostat 120 mg/day group, and a causal relationship with the study drug was ruled out. Adverse events leading to study discontinuation occurred in 1 subject (gout arthritis/blood lactate dehydrogenase increased/γ-glutamyltransferase (γ-GTP) increased/blood alkaline phosphatase increased/ALT increased/AST increased) in the topiroxostat 80 mg/day group, 1 subject (cholelithiasis/NAG increased/β2 microglobulin increased) in the topiroxostat 120 mg/day group, and 1 subject (thirst) in the topiroxostat 160 mg/day group. All events except “cholelithiasis” and “β2 microglobulin increased” were classified as adverse drug reactions.

The incidence of gout arthritis in each treatment period is shown in Table 31. The incidence of gout arthritis was 6.8% (5 of 74 subjects) during the initial phase (40 mg/day), and after the subsequent dose increase (i.e. to 80 mg/day, 120 mg/day, or 160 mg mg/day), the incidence at the end of treatment was 4.3% (1 of 23 subjects) in the topiroxostat 80 mg/day group, 4.3% (1 of 23 subjects) in the topiroxostat 120 mg/day group, and 13.0% (3 of 23 subjects) in the topiroxostat 160 mg/day group.

Table 31. Incidence of gout arthritis by treatment time point (Study FYX-051-222, safety analysis set)

Time point	Topiroxostat 80 mg/day group	Topiroxostat 120 mg/day group	Topiroxostat 160 mg/day group
Week 2	8.3 (2/24)	4.0 (1/25)	8.0 (2/25)
Week 4	0.0 (0/23)	8.3 (2/24)	0.0 (0/24)
Week 8	4.3 (1/23)	4.3 (1/23)	4.3 (1/23)
Week 12	4.3 (1/23)	4.3 (1/23)	13.0 (3/23)
Overall period	16.7 (4/24)	12.0 (3/25)	20.0 (5/25)

% incidence (number of subjects with events/number of analyzed subjects)

There were no clinically relevant changes in vital signs and 12-lead ECG.

4.(iii).A.(2).3) Late phase II study (5.3.5.1-3, Study FYX-051-323, [redacted] 20[redacted] to [redacted] 20[redacted])

A randomized, placebo-controlled, double-blind, parallel-group study was conducted with allopurinol as the reference treatment in Japanese patients with hyperuricaemia including gout[48] (target number of subjects, 160 subjects) to evaluate the efficacy and safety of the drug product.

This study consisted of a run-in period (1 to 4 weeks) and a treatment period (initial phase I, 2 weeks; initial phase II, 4 weeks; maintenance phase, 10 weeks).

The placebo group received the placebo orally twice daily after the morning and evening meals throughout the treatment period. The topiroxostat groups received topiroxostat orally twice daily after the morning and evening meals. The dosage in the topiroxostat 120 and 160 mg groups was 20 mg/dose (40 mg/day) in both groups during the 2 weeks of initial phase I, 40 mg/dose (80 mg/day) in both groups during the 4 weeks of initial phase II, and 60 mg/dose (120 mg/day) and 80 mg/dose (160 mg/day), respectively, during the 10 weeks of the maintenance phase. The allopurinol group received 100 mg of oral allopurinol once daily (100 mg/day) after the morning meal (placebo after the evening meal) during the 2 weeks of initial phase I and 100 mg of oral allopurinol twice daily (200 mg/day) after the morning and evening meals throughout initial phase II and the maintenance phase (14 weeks in total).[49]

All 157 treated subjects (39 in the placebo group, 39 in the topiroxostat 120 mg/day group, 40 in the topiroxostat 160 mg/day group, 39 in the allopurinol group) were included in the safety analysis set. The FAS included 156 subjects excluding 1 subject in the allopurinol group.[50] The FAS was defined as the efficacy analysis set. The study was discontinued in 7 subjects, including 5 subjects (adverse events, 3 subjects; progression of the primary disease, 1 subject; consent withdrawal, 1 subject) in the placebo group, 1 subject (consent withdrawal) in the topiroxostat 160 mg/day group, and 1 subject (protocol non-compliance) in the allopurinol group.

The efficacy in terms of the primary endpoint, i.e. percentage decrease in serum uric acid level from baseline at the end of treatment in the FAS, is shown in Table 32. The Jonckheere-Terpstra test detected statistical significance ($P < 0.001$, a two-sided significance level of 5%) in the placebo group and the topiroxostat 120 mg/day and 160 mg/day groups.

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[48] Major inclusion criteria: Japanese patients with hyperuricaemia including gout; aged ≥20 and <65 years at the time of informed consent; serum uric acid level in the run-in period of ≥7.0 mg/dL in patients with tophi or a history of gout attacks or ≥9.0 mg/dL in patients with hyperuricaemia (however, ≥8.0 mg/dL in patients who were receiving treatment for or had a diagnosis of urolithiasis, hypertension, hyperlipidemia, or diabetes). A 2 to 4-week washout period was set before the run-in period for subjects who received drugs that affect the serum uric acid level (including drugs for gout and hyperuricaemia). Patients showing primary or secondary hyperuricaemia were excluded.

[49] When gout arthritis occurred Weeks 2, 6, or 16, the dose during the preceding phase could be continued for up to 1 week.

[50] Emergency code breaking took place because of death by suicide.

Table 32. Percentage decrease in serum uric acid level from baseline at the end of treatment (FYX-051-323, FAS)

	Placebo group (n = 39)	Topiroxostat 120 mg/day group (n = 39)	Topiroxostat 160 mg/day group (n = 40)	Allopurinol group (n = 38)
Serum uric acid level at baseline (mg/dL)	9.01 ± 1.17 (n = 39)	9.07 ± 1.38 (n = 39)	9.00 ± 1.19 (n = 40)	9.24 ± 1.60 (n = 38)
Serum uric acid level at the end of treatment (mg/dL)[a)]	8.63 ± 1.37 (n = 35)	5.36 ± 1.19 (n = 39)	4.96 ± 1.19 (n = 39)	5.43 ± 0.75 (n = 38)
Percentage decrease in serum uric acid level from baseline at the end of treatment [a)] (%)	3.93 ± 11.39 (n = 35)	40.92 ± 9.84 (n = 39)	44.79 ± 13.26 (n = 39)	40.18 ± 10.30 (n = 38)
P-value[b)]	$P < 0.001$		-	
Percentage decrease in serum uric acid level from baseline at the end of treatment[c)] (%) (LOCF)	3.66 ± 11.60 (n = 39)	40.92 ± 9.84 (n = 39)	44.09 ± 13.82 (n = 40)	40.18 ± 10.30 (n = 38)

Mean ± SD; –, not applicable

a) It was decided that, when the measurement at 16 weeks post-dose was missing, the measurement at 14 weeks post-dose would be used for evaluation of the measurement at the end of study drug administration. Among subjects withdrawn from the study, 3 subjects with data only up to 10 weeks post-dose (2 subject in the placebo group, 1 subject in the topiroxostat 160 mg/day group), 1 subject with data only up to 6 weeks post-dose (placebo group), and 1 subject with data only up to 2 weeks post-dose (placebo group) were excluded from analysis.

b) Jonckheere-Terpstra test with a two-sided significance level of 5%

c) The results of subjects excluded from analysis in a) were imputed by LOCF. However, 1 subject in the allopurinol group was excluded from analysis because post-dose data were missing. Results of post-hoc analysis.

The results for the secondary endpoint, i.e. time course of serum uric acid levels, are shown in Table 33.

Table 33. Time course of serum uric acid levels (Study FYX-051-323, FAS)

Time point of evaluation	Placebo group	Topiroxostat 120 mg/day group	Topiroxostat 160 mg/day group	Allopurinol group
Baseline	9.01 ± 1.17 (n = 39)	9.07 ± 1.38 (n = 39)	9.00 ± 1.19 (n = 40)	9.24 ± 1.60 (n = 38)
Week 2[a)]	8.77 ± 1.04 (n = 39)	6.78 ± 1.31 (n = 39)	6.82 ± 1.14 (n = 40)	7.07 ± 1.06 (n = 36)
Week 6[b)]	8.79 ± 1.22 (n = 38)	5.86 ± 1.05 (n = 39)	5.89 ± 0.92 (n = 40)	5.65 ± 1.02 (n = 36)
Week 10	8.86 ± 1.00 (n = 37)	5.29 ± 1.01 (n = 38)	4.94 ± 1.01 (n = 40)	5.64 ± 1.12 (n = 37)
Week 14	8.51 ± 1.13 (n = 35)	5.44 ± 1.16 (n = 38)	4.83 ± 0.98 (n = 37)	5.34 ± 0.79 (n = 38)
Week 16	8.66 ± 1.40 (n = 33)	5.38 ± 1.20 (n = 38)	4.96 ± 1.19 (n = 39)	5.43 ± 0.75 (n = 38)
End of treatment	8.63 ± 1.37 (n = 35)	5.36 ± 1.19 (n = 39)	4.96 ± 1.19 (n = 39)	5.43 ± 0.75 (n = 38)

Unit, mg/dL; mean ± SD

a) Values during the period when a 20 mg dose was administered twice daily (40 mg/day) in the topiroxostat groups, and values when a 100 mg dose was administered once daily in the allopurinol group.

b) Values during the period when a 40 mg dose was administered twice daily (80 mg/day) after the second week of treatment in the topiroxostat groups, and when a 200 mg dose was administered once daily in the allopurinol group.

The percentage of subjects who achieved the target serum uric acid level of ≤6.0 mg/dL at the end of treatment is shown in Table 34.

Table 34. Percentage of subjects achieving a serum uric acid level of ≤6.0 mg/dL at the end of treatment (Study FYX-051-323, FAS)

	Placebo group (n = 35)	Topiroxostat 120 mg/day group (n = 39)	Topiroxostat 160 mg/day group (n = 39)	Allopurinol group (n = 38)
Percentage of subjects achieving a serum uric acid level of ≤6.0 mg/dL (number of subjects achieving ≤6.0 mg/dL)	0.0 (0)	76.9 (30)	76.9 (30)	84.2 (32)
95% CI	[0.00, 8.20]	[60.67, 88.87]	[60.67, 88.87]	[68.75, 93.98]

Safety results showed the following cumulative incidence of adverse events at the end of treatment: 74.4% (29 of 39 subjects) in the placebo group, 71.8% (28 of 39 subjects) in the topiroxostat 120 mg/day group, 62.5% (25 of 40 subjects) in the topiroxostat 160 mg/day group, and 59.0% (23 of 39 subjects) in the allopurinol group. The incidence of adverse drug reactions was 38.5% (15 of 39 subjects) in the placebo group, 20.5% (8 of 39 subjects) in the topiroxostat 120 mg/day group, 17.5% (7 of 40 subjects) in the topiroxostat 160 mg/day group, and 25.6 % (10 of 39 subjects) in the

allopurinol group. The adverse events and/or adverse drug reactions reported in ≥5% of subjects in any treatment group are shown in Table 35.

Table 35. Adverse events and/or adverse drug reactions reported in ≥5% of subjects in any treatment group (Study FYX-051-323, safety analysis set)

Name of event	Placebo group (n = 39)		Topiroxostat 120 mg/day group (n = 39)		Topiroxostat 160 mg/day group (n = 40)		Allopurinol group (n = 39)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
Any event	74.4 (29)	38.5 (15)	71.8 (28)	20.5 (8)	62.5 (25)	17.5 (7)	59.0 (23)	25.6 (10)
Nasopharyngitis	25.6 (10)	0.0 (0)	7.7 (3)	0.0 (0)	27.5 (11)	0.0 (0)	12.8 (5)	0.0 (0)
ALT increased	10.3 (4)	5.1 (2)	5.1 (2)	0.0 (0)	10.0 (4)	7.5 (3)	10.3 (4)	7.7 (3)
AST increased	7.7 (3)	5.1 (2)	5.1 (2)	0.0 (0)	12.5 (5)	7.5 (3)	7.7 (3)	5.1 (2)
β2 microglobulin urine increased	0.0 (0)	0.0 (0)	5.1 (2)	0.0 (0)	5.0 (2)	0.0 (0)	2.6 (1)	0.0 (0)
NAG increased	2.6 (1)	0.0 (0)	5.1 (2)	2.6 (1)	5.0 (2)	0.0 (0)	15.4 (6)	5.1 (2)
Blood creatine phosphokinase increased	7.7 (3)	5.1 (2)	12.8 (5)	0.0 (0)	15.0 (6)	2.5 (1)	10.3 (4)	0.0 (0)
Blood triglycerides increased	7.7 (3)	0.0 (0)	2.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
γ-GTP increased	15.4 (6)	5.1 (2)	5.1 (2)	0.0 (0)	7.5 (3)	2.5 (1)	5.1 (2)	2.6 (1)
Blood urine present	5.1 (2)	0.0 (0)	2.6 (1)	2.6 (1)	5.0 (2)	0.0 (0)	0.0 (0)	0.0 (0)
White blood cell count decreased	7.7 (3)	0.0 (0)	2.6 (1)	2.6 (1)	0.0 (0)	0.0 (0)	5.1 (2)	0.0 (0)
α1microglobulin urine increased	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	7.5 (3)	0.0 (0)	0.0 (0)	0.0 (0)
Arthralgia	5.1 (2)	0.0 (0)	2.6 (1)	0.0 (0)	2.5 (1)	0.0 (0)	7.7 (3)	2.6 (1)
Back pain	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	5.0 (2)	0.0 (0)	0.0 (0)	0.0 (0)
Pain in extremity	10.3 (4)	10.3 (4)	10.3 (4)	5.1 (2)	2.5 (1)	2.5 (1)	2.6 (1)	2.6 (1)
Headache	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	2.5 (1)	0.0 (0)	5.1 (2)	0.0 (0)
Eczema	5.1 (2)	2.6 (1)	2.6 (1)	0.0 (0)	2.5 (1)	0.0 (0)	0.0 (0)	0.0 (0)
Gout arthritis	7.7 (3)	7.7 (3)	5.1 (2)	5.1 (2)	5.0 (2)	5.0 (2)	10.3 (4)	10.3 (4)

% incidence (number of subjects with events), MedDRA/J (ver. 13.0)

One subject in the allopurinol group died (completed suicide), but a causal relationship with the study drug was ruled out. The only other severe adverse event was “nephrolithiasis” (1 subject, 1 event) in 1 subject in the placebo group, but a causal relationship with the study drug was ruled out. Adverse events leading to study discontinuation included 7 events in 4 subjects in the placebo group (nephrolithiasis, limb discomfort/gout arthritis, ALT increased/AST increased/γ-GTP increased, eczema) and 1 event in 1 subject (completed suicide [death]) in the allopurinol group. The events other than “nephrolithiasis” and “completed suicide” were classified as adverse drug reactions.

The incidence of gout arthritis in each treatment period is shown in Table 36.

Table 36. Incidence of gout arthritis by treatment time point (Study FYX-051-323, safety analysis set)

Time point	Placebo group	Topiroxostat 120 mg/day group	Topiroxostat 160 mg/day group	Allopurinol group
Week 2	5.1 (2/39)	0.0 (0/39)	0.0 (0/40)	0.0 (0/39)
Week 6	2.6 (1/39)	0.0 (0/39)	0.0 (0/40)	5.1 (2/39)
Week 10	0.0 (0/37)	2.6 (1/39)	2.5 (1/40)	5.1 (2/39)
Week 14	0.0 (0/36)	2.6 (1/39)	2.5 (1/40)	5.3 (2/38)
Week 16	0.0 (0/34)	0.0 (0/39)	0.0 (0/39)	2.6 (1/38)
Overall period	7.7 (3/39)	5.1 (2/39)	5.0 (2/40)	10.3 (4/39)

% incidence (number of subjects with events/number of analyzed subjects)

There were no clinically relevant changes in vital signs and 12-lead ECG.

4.(iii).A.(3) Phase III study

4.(iii).A.(3).1) Phase III study (5.3.5.1-4: Study FY1001 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, double-blind, parallel-group, active-controlled study was conducted in Japanese patients with hyperuricaemia including gout[51] (target number of subjects, 200) to evaluate the efficacy and safety of topiroxostat compared with allopurinol as the active control.

This study consisted of a run-in period (1 to 4 weeks) and a treatment period (initial phase I, 2 weeks; initial phase II, 4 weeks; maintenance phase, 10 weeks).

The topiroxostat group received topiroxostat orally twice daily after the morning and evening meals. The dosage was 20 mg/dose (40 mg/day) during the 2 weeks of initial phase I, 40 mg/dose (80 mg/day) during the 4 weeks of initial phase II, and 60 mg/dose (120 mg/day) during the 10 weeks of the maintenance phase. The allopurinol group received 100 mg of oral allopurinol once daily (100 mg/day) after the morning meal and the placebo after the evening meal during the 2 weeks of initial phase I and 100 mg of oral allopurinol twice daily (200 mg/day) after the morning and evening meals throughout initial phase II and the maintenance phase (14 weeks in total).[52]

All 205 treated subjects (100 in the topiroxostat group, 105 in the allopurinol group) were included in the safety analysis set. Of these, 203 subjects (98 in the topiroxostat group, 105 in the allopurinol group), excluding 2 subjects with missing results of blood tests after study drug administration, were included in the FAS. The FAS was defined as the efficacy analysis set. The study was discontinued in the following subjects: 2 subjects (adverse events) in the topiroxostat group and 1 subject (adverse events) in the allopurinol group during initial phase I; 2 subjects (consent withdrawal and other reason, 1 subject each) in the topiroxostat group and 2 subjects (consent withdrawal and no study visit, 1 subject each) in the allopurinol group during initial phase II; 5 subjects (adverse events, 4 subjects; consent withdrawal, 1 subject) in the topiroxostat group and 7 subjects (adverse events, 5 subjects; no study visit, 1 subject; other reason, 1 subject) in the allopurinol group during the maintenance phase.

The efficacy in terms of the primary endpoint, i.e. percentage decrease in serum uric acid level from baseline at the end of treatment in the FAS, shown in Table 37, demonstrated the non-inferiority of the topiroxostat group compared with the allopurinol group ($P < 0.0001$, non-inferiority t-test with a non-inferiority limit of 8% and a two-sided significance level of 5%).

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[51] Major inclusion criteria: Japanese patients with hyperuricaemia including gout; aged ≥20 and <75 at the time of informed consent; serum uric acid level in the run-in period of ≥7.0 mg/dL in patients with tophi or a history of gouty attacks or ≥9.0 mg/dL in patients with hyperuricaemia (≥8.0 mg/dL in patients receiving treatment for or with a diagnosis of urolithiasis, hypertension, hyperlipidemia, or diabetes). A washout period of not less than 2 weeks was provided before the run-in period for subjects who had taken drugs that affect serum uric acid level (including drugs for gout and hyperuricaemia). Patients showing primary or secondary hyperuricaemia were excluded.

[52] If gout arthritis that occurred during initial phase I or II did not disappear after 2 or 6 weeks, respectively, of administration, the same dose could be continued without dose escalation until disappearance of gout arthritis, for a maximum of 1 additional week from the day specified for each time point (until Day 22 after 2-week administration, until Day 50 after 6-week administration). The study was discontinued if gout arthritis did not disappear within a maximum of 1 week. If gout arthritis was noted at Week 16 (the last day of treatment), study drug administration was continued for a maximum of 1 additional week (until Day 120), in principle until disappearance of gout arthritis, and was discontinued if gout arthritis did not disappear within a maximum of 1 week.

Table 37. Percentage decrease in serum uric acid level from baseline at the end of treatment (Study FY1001, FAS)

	Topiroxostat group (n = 98)	Allopurinol group (n = 105)
Baseline serum uric acid level (mg/dL)	8.62 ± 1.08	8.50 ± 0.96
Serum uric acid level at the end of treatment	5.47 ± 1.20	5.57 ± 1.04
Percentage decrease in serum uric acid level from baseline at the end of treatment (%)	36.28 ± 12.65	34.26 ± 11.08
Two-sided 95% CI	[33.75, 38.82]	[32.12, 36.41]
P-value[a)]	*P* < 0.0001	
Between-group difference and two-sided 95% CI [Topiroxostat group - allopurinol group]	2.02[-1.26, 5.31]	

Mean ± SD, LOCF

a) Non-inferiority t-test with a non-inferiority limit of 8% and a two-sided significance level of 5%

The results for the secondary endpoint, i.e. time course of serum uric acid levels, are shown in Table 38.

Table 38. Time course of serum uric acid levels (Study FY1001, FAS)

Timing of evaluation	Topiroxostat group	Allopurinol group
Baseline	8.62 ± 1.08 (n = 98)	8.50 ± 0.96 (n = 105)
Week 2[a)]	6.58 ± 1.05 (n = 97)	6.77 ± 0.82 (n = 105)
Week 6[b)]	5.92 ± 1.15 (n = 96)	5.53 ± 0.91 (n = 104)
Week 10	5.45 ± 1.14 (n = 93)	5.55 ± 1.01 (n = 100)
Week 14	5.49 ± 1.27 (n = 92)	5.49 ± 0.99 (n = 96)
Week 16	5.46 ± 1.23 (n = 91)	5.52 ± 0.98 (n = 93)

Unit, mg/dL; mean ± SD

a) Values during the period when a 20 mg dose was administered twice daily (40 mg/day) in the topiroxostat groups, and values during the period when a 100 mg dose was administered once daily in the allopurinol group.

b) Values during the period when a 40 mg dose was administered twice daily (80 mg/day) after the second week of treatment in the topiroxostat groups, and values during the period when a 200 mg dose was administered once daily in the allopurinol group.

The percentage of subjects who achieved the target serum uric acid level of ≤6.0 mg/dL at the end of treatment is shown in Table 39.

Table 39. Percentage of subjects achieving a serum uric acid level of ≤6.0 mg/dL at the end of treatment (Study FY1001, FAS)

	Topiroxostat group (n = 98)	Allopurinol group (n = 105)
Percentage of subjects achieving a serum uric acid level of ≤6.0 mg/dL (number of subjects achieving ≤6.0 mg/dL)	72.4 (71)	73.3 (77)
95% CI	[62.5, 81.0]	[63.8, 81.5]

Safety results showed the following cumulative incidence of adverse events at the end of treatment: 97.0% (97 of 100 subjects) in the topiroxostat group and 93.3% (98 of 105 subjects) in the allopurinol group. The incidence of adverse drug reactions was 36.0% (36 of 100 subjects) in the topiroxostat group and 27.6 % (29 of 105 subjects) in the allopurinol group. The adverse events and/or adverse drug reactions reported in ≥5% of subjects in any treatment group are shown in Table 40.

Table 40. Adverse events and/or adverse drug reactions reported in ≥5% of subjects in any treatment group (Study FY1001, safety analysis set)

Name of event	Topiroxostat group (n = 100)		Allopurinol group (n = 105)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
Any event	97.0 (97)	36.0 (36)	93.3 (98)	27.6 (29)
Bronchitis	5.0 (5)	0.0 (0)	2.9 (3)	0.0 (0)
Nasopharyngitis	10.0 (10)	0.0 (0)	9.5 (10)	0.0 (0)
Gout arthritis	12.0 (12)	11.0 (11)	7.6 (8)	6.7 (7)
ALT increased	24.0 (24)	12.0 (12)	7.6 (8)	2.9 (3)
AST increased	24.0 (24)	6.0 (6)	11.4 (12)	2.9 (3)
β2 microglobulin increased	16.0 (16)	6.0 (6)	15.2 (16)	4.8 (5)
β2 microglobulin urine increased	16.0 (16)	4.0 (4)	22.9 (24)	3.8 (4)
NAG increased	25.0 (25)	7.0 (7)	20.0 (21)	1.9 (2)
Blood amylase increased	6.0 (6)	1.0 (1)	10.5 (11)	1.0 (1)
Blood cholesterol increased	9.0 (9)	0.0 (0)	6.7 (7)	0.0 (0)
Blood creatine phosphokinase increased	17.0 (17)	3.0 (3)	15.2 (16)	2.9 (3)
Blood lactate dehydrogenase increased	9.0 (9)	2.0 (2)	7.6 (8)	1.0 (1)
Blood triglycerides increased	42.0 (42)	0.0 (0)	38.1 (40)	0.0 (0)
γ-GTP increased	15.0 (15)	2.0 (2)	4.8 (5)	1.9 (2)
Blood urine present	7.0 (7)	2.0 (2)	2.9 (3)	0.0 (0)
White blood cell count increased	5.0 (5)	0.0 (0)	10.5 (11)	1.9 (2)
Blood phosphorus decreased	2.0 (2)	0.0 (0)	5.7 (6)	1.0 (1)
Eosinophil percentage increased	5.0 (5)	0.0 (0)	6.7 (7)	0.0 (0)
Monocyte percentage increased	7.0 (7)	0.0 (0)	2.9 (3)	0.0 (0)
Lymphocyte percentage decreased	5.0 (5)	0.0 (0)	5.7 (6)	1.0 (1)
Protein urine present	2.0 (2)	0.0 (0)	6.7 (7)	1.9 (2)
α1 microglobulin urine increased	34.0 (34)	8.0 (8)	31.4 (33)	5.7 (6)
Blood creatine phosphokinase decreased	5.0 (5)	1.0 (1)	1.0 (1)	0.0 (0)

% incidence (number of subjects with events), MedDRA/J (ver. 13.0)

One subject in the allopurinol group died (cardiac hypertrophy), but a causal relationship with the study drug was ruled out. Two other serious adverse events (prostate cancer, colonic polyp) occurred in 2 subjects in the topiroxostat group, but a causal relationship with the study drug was ruled out in both cases. Adverse events leading to study discontinuation included 5 events in 5 subjects of the topiroxostat group (rash, 2 subjects; drug eruption, β2 microglobulin urine increased, and abdominal pain upper, 1 subject each) and 7 events in 6 subjects in the allopurinol group (gout arthritis, 2 subjects; cardiac hypertrophy [death], rhabdomyolysis, ALT increased/AST increased, and urticaria, 1 subject each), and "gout arthritis" and "rhabdomyolysis" were classified as adverse drug reactions.

Gout arthritis occurred with an incidence of 12.0% (12 of 100 subjects) in the topiroxostat group and 7.6% (8 of 105 subjects) in the allopurinol group. The incidence of gout arthritis in each treatment period is shown in Table 41.

Table 41. Incidence of gout arthritis by treatment time point (Study FY1001, safety analysis set)

Time point	Topiroxostat group (n = 100)	Allopurinol group (n = 105)
Initial phase I	2.0 (2/100)	1.9 (2/105)
Initial phase II	1.0 (1/97)	3.8 (4/104)
Week 4 in maintenance phase	5.2 (5/97)	2.0 (2/102)
Week 8 in maintenance phase	4.3 (4/94)	1.0 (1/98)
Week 10 in maintenance phase	1.1 (1/92)	0.0 (0/96)
>Week 10 in maintenance phase	1.1 (1/92)	0.0 (0/96)
Overall period	12.0 (12/100)	7.6 (8/105)

% incidence (number of subjects with events/number of analyzed subjects)

Vital sign changes included abnormal changes in blood pressure[53] in 1 subject of the allopurinol group. There were no clinically relevant changes in 12-lead ECG.

[53] A case outside the normal range (systolic blood pressure, ≥ 90 mmHg and < 140 mmHg; diastolic blood pressure, < 90 mmHg).

4.(iii).A.(3).2) Six-month treatment study (5.3.5.1-5: Study FYX-051-332, [redacted] 20[redacted] to [redacted] 20[redacted])

An open-label study was conducted in Japanese patients with hyperuricaemia including gout[54] (target number of subjects, 230) to evaluate the efficacy and safety of topiroxostat in long-term treatment.

This study consisted of a run-in period (1 to 4 weeks) and a treatment period (initial phase I, 2 weeks; initial phase II, 4 weeks; maintenance phase I, 12 weeks; maintenance phase II, 12 weeks).

The subjects received topiroxostat orally twice daily after the morning and evening meals. The dosage was 20 mg/dose (40 mg/day) during the 2 weeks of initial phase I, 40 mg/dose (80 mg/day) during the 4 weeks of initial phase II, and 60 mg/dose (120 mg/day) during the 12 weeks of maintenance phase I. The dose administered in maintenance phase I was maintained for 12 weeks in maintenance phase II when the serum uric acid level was ≤6.0 mg/dL at Week 14. Otherwise, 80 mg of topiroxostat was orally administered twice daily (160 mg/day) after the morning and evening meals for 12 weeks when the serum uric acid level was not ≤6.0 mg/dL at Week 14. When gout arthritis occurred at Week 2, 6, 18, or 30, the dose during the preceding phase was allowed to be maintained for up to 1 week.

All 240 treated subjects were included in the safety analysis set and the FAS, and the FAS was defined as the efficacy analysis set. The study was discontinued in 2 subjects (adverse events and consent withdrawal, 1 subject each) during initial phase I, 7 subjects (adverse event and consent withdrawal, 2 subjects each; protocol non-compliance, progression of the primary disease, and treatment of complications, 1 subject each) during initial phase II, 10 subjects (adverse events, 9 subject; protocol non-compliance, 1 subject) during maintenance phase I, and 5 subjects (adverse events, 3 subject; consent withdrawal and protocol non-compliance, 1 subject each) during maintenance phase II. Of 221 subjects who entered maintenance phase II, the dose was maintained at 120 mg/day in 163 subjects, while it was increased to 160 mg/day in 58 subjects during maintenance phase II, and study drug administration was completed in 159 and 57 subjects, respectively.

The efficacy in terms of the primary endpoint, i.e. percentage decrease in serum uric acid level from baseline at the end of treatment in the FAS (mean ± SD [95% CI]), was 39.23% ± 12.12% [37.68, 40.77].

The results for the secondary endpoint, i.e. time course of serum uric acid levels, are shown in Figure 1.

[54] Major inclusion criteria: Japanese patients with hyperuricaemia including gout; aged ≥20 and <75 years at the time of informed consent; serum uric acid level in the run-in period of ≥7.0 mg/dL in patients with tophi or a history of gout attacks or ≥9.0 mg/dL in patients with hyperuricaemia (≥8.0 mg/dL in patients receiving treatment for or with a diagnosis of urolithiasis, hypertension, hyperlipidemia, or diabetes). A washout period of ≥2 weeks was provided before the run-in period for subjects who had taken drugs that affect serum uric acid level (including drugs for gout and hyperuricaemia). Patients showing primary or secondary hyperuricaemia were excluded.

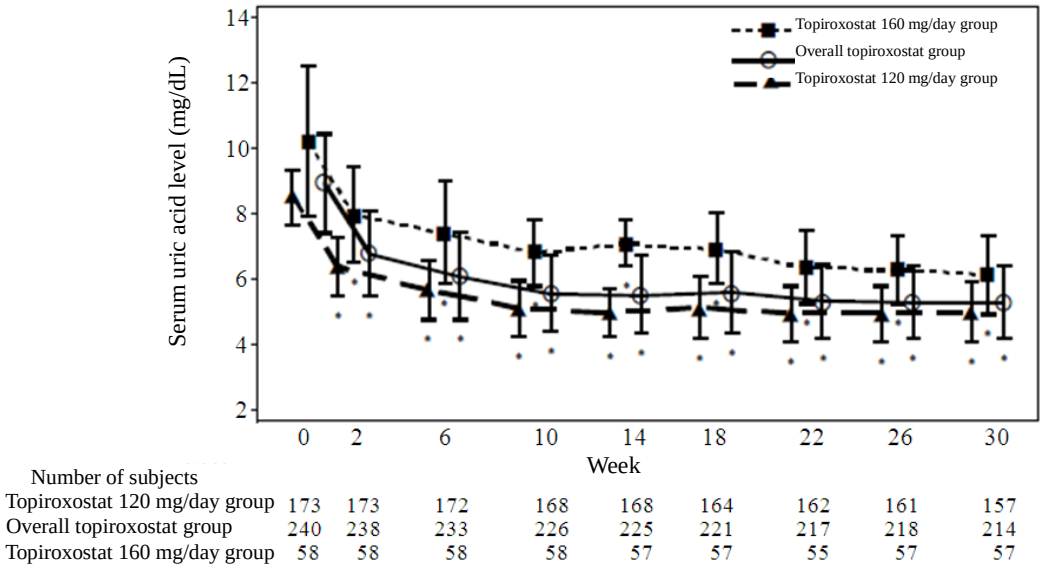


Figure 1. Time course of serum uric acid levels from the start of treatment (FYX-051-332 study, FAS, mean ± SD)

The percentage of subjects who achieved the target serum uric acid level of ≤6.0 mg/dL was 69.2% (153 of 221 subjects) at Week 18 (before dose increase) and 76.9% (183 of 238 subjects) at the end of treatment. The percentage of subjects who achieved the target serum uric acid level of ≤6.0 mg/dL at the end of treatment was 62.6% (149 of 238 subjects) in the 120 mg/day group and 83.2% (198 of 238 subjects) in a combination of subjects who achieved the target serum uric acid level of ≤ 6.0 mg/dL either at Week 14 at the final dose of 120 mg/day or after a dose increase to 160 mg/day.

Safety results showed the following cumulative incidence at the end of treatment: 84.6% (203 of 240 subjects) for adverse events and 26.7% (64 of 240 subjects) for adverse drug reactions. The adverse events and/or adverse drug reactions reported in ≥5% of subjects are shown in Table 42.

Table 42. Adverse events and/or adverse drug reactions reported in ≥5% of subjects (Study FYX-051-332, safety analysis set)

Name of event	Topiroxostat group (n = 240)	
	Adverse event	Adverse drug reaction
All events	84.6 (203)	26.7 (64)
Nasopharyngitis	22.9 (55)	0.0 (0)
Gout arthritis	12.1 (29)	12.1 (29)
Pain in extremity	6.3 (15)	1.3 (3)
ALT increased	20.4 (49)	5.8 (14)
AST increased	12.9 (31)	2.9 (7)
β2 microglobulin urine increased	15.4 (37)	2.1 (5)
NAG increased	20.0 (48)	3.3 (8)
Blood creatine phosphokinase increased	11.3 (27)	1.3 (3)
Blood pressure increased	5.4 (13)	0.0 (0)
Blood triglycerides increased	10.0 (24)	0.0 (0)
γ-GTP increased	8.3 (20)	0.8 (2)
α1 microglobulin increased	9.6 (23)	0.4 (1)

% incidence (number of subjects with events), MedDRA/J (ver. 14.0)

No deaths occurred, while the following 10 serious adverse events occurred in 9 subjects: “cerebral infarction” in 1 subject during initial phase I (40 mg/day); “calculus urinary” in 2 subjects and “colitis ulcerative, ” “inguinal hernia, ” “AST increased/ALT increased, ” and “liver disorder” in 1 patient

each during maintenance phase I (120 mg/day); and "cholecystitis" and "erythema multiforme" in 1 subject each during maintenance phase II (160 mg/day). "AST increased/ALT increased," "liver disorder," and "erythema multiforme" were classified as adverse drug reactions. Adverse events leading to study discontinuation occurred in 18 subjects (53 events), including 2 subjects (cerebral infarction, panic attack) during initial phase I (40 mg/day), 4 subjects (gout arthritis, gout arthritis/gingival bleeding/oral pain/β2 microglobulin urine increased/NAG increased/blood amylase increased/eosinophilia/α1 microglobulin increased, oropharyngeal discomfort, platelet count increased/NAG increased/cellulitis) during initial phase II (80 mg/day), 10 subjects (colitis ulcerative, inguinal hernia, calculus urinary/cystatin C increased/α1 microglobulin increased/β2 microglobulin increased/NAG increased/blood creatinine increased/blood urea increased/C-reactive protein increased/blood urine present/platelet count decreased/red blood cells urine positive/white blood cells urine positive, liver disorder/ALT increased/AST increased, urticaria, ALT increased, arthralgia/pain in extremity, blood creatinine increased/drug eruption/β2 microglobulin urine increased/NAG increased, erythema, eczema) during maintenance phase I (120 mg/day), and 2 subjects (blood phosphorus decreased/α1 microglobulin increased/white blood cell count increased/cholecystitis/C-reactive protein increased/lymphocyte count decreased/neutrophil count increased/NAG increased, benign prostatic hyperplasia/hepatic steatosis) during maintenance phase II (120 mg/day). The following adverse events were classified as adverse drug reactions: "gout arthritis," "gout arthritis/gingival bleeding/oral pain/β2 microglobulin urine increased/NAG increased/blood amylase increased/eosinophilia/α1 microglobulin increased," and "platelet count increased/NAG increased" during initial phase II and "liver disorder/ALT increased/AST increased," "urticaria," "blood creatinine increased/drug eruption/β2 microglobulin urine increased/NAG increased," and "erythema" during maintenance phase I.

The incidence of gout arthritis in each treatment period is shown in Table 43. Six cases of gout arthritis during maintenance phase II occurred in 4 of 163 subjects (2.5%) treated at the maintained dose of 120 mg/day and 4 cases occurred in 4 of 58 subjects (6.9%) treated at the increased dose of 160 mg/day.

Table 43. Incidence of gout arthritis by treatment time point (Study FYX-051-332, safety analysis set)

Time point	All topiroxostat groups	Topiroxostat 120 mg/day group[a)]	Topiroxostat 160 mg/day group[a)]	Topiroxostat <120 mg/day group[a)]
Initial phase I (2 weeks)	2.9 (7/240)	3.5 (6/173)	1.7 (1/58)	0.0 (0/9)
Initial phase II (4 weeks)	3.8 (9/238)	2.9 (5/173)	3.4 (2/58)	28.6 (2/7)
Maintenance phase I (12 weeks)	6.1 (14/231)	5.2 (9/173)	8.6 (5/58)	–
Maintenance phase II (12 weeks)	3.6 (8/221)	2.5 (4/163)	6.9 (4/58)	–
Overall period	12.1 (29/240)	10.4 (18/173)	15.5 (9/58)	22.2 (2/9)

% incidence (number of subjects with events/number of analyzed subjects); –, not applicable
a) Final dose level

Changes in vital signs and 12-lead ECG included abnormal changes in blood pressure[53] in 13 of 240 subjects (5.4%) and abnormal changes in ECG in 2 of 240 subjects (0.8%).

4.(iii).A.(3).3) Fifty-eight-week treatment study (5.3.5.1-6, Study FY1002, [redacted] 20[redacted] to [redacted] 20[redacted])

An open-label study was conducted in Japanese patients with hyperuricaemia including gout[55] (target number of subjects, 115) to evaluate the efficacy and safety of long-term topiroxostat treatment.

This study consisted of a run-in period (1 to 4 weeks) and a treatment period (initial phase I, 2 weeks; initial phase II, 4 weeks; maintenance phase I, 12 weeks; maintenance phase II, 40 weeks).

The subjects received topiroxostat orally twice daily after the morning and evening meals. The dosage was 20 mg/dose (40 mg/day) during the 2 weeks of initial phase I, 40 mg/dose (80 mg/day) during the 4 weeks of initial phase II, and 60 mg/dose (120 mg/day) during the 12 weeks of maintenance phase. The dose in maintenance phase I was maintained for 40 weeks in maintenance phase II when the serum uric acid level was ≤6.0 mg/dL at Week 14. When the serum uric acid level was not ≤6.0 mg/dL, twice-daily oral administration of 80 mg of topiroxostat (160 mg/day) after the morning and evening meals was started at Week 18 and continued for 40 weeks. When the serum uric acid level was not ≤6.0 mg/dL at Week 26 (8 weeks after the dose increase to 160 mg/day), twice-daily oral administration of 100 mg of topiroxostat (200 mg/day) after the morning and evening meals was started at Week 30. When the serum uric acid level was not ≤6.0 mg/dL at Week 38 (8 weeks after the dose increase to 200 mg/day), twice-daily oral administration of 120 mg of topiroxostat (240 mg/day) after the morning and evening meals was started at Week 42. When the serum uric acid level was ≤6.0 mg/dL at Weeks 14 and 26, the dose was not increased even if the serum uric acid level exceeded 6.0 mg/dL at the subsequent time points to assess the applicability of dose increase. When gout arthritis occurred at Week 2, 6, 18, 30, or 42, the dose during the preceding phase was allowed to be maintained for up to 1 week.

All 121 treated subjects were included in the safety analysis set and the FAS, and the FAS was defined as the efficacy analysis set. The study was discontinued in 3 subjects (consent withdrawal, protocol non-compliance, and adverse events, 1 subject each) during initial phase I (40 mg/day), 3 subjects (adverse events, 2 subjects; consent withdrawal, 1 subject) during initial phase II (80 mg/day), 5 subjects (adverse events, 3 subjects; consent withdrawal, 1 subject; others, 1 subject) during maintenance phase I (120 mg/day), and 6 subjects (adverse events, 5 subjects; consent withdrawal, 1 subject) during maintenance phase II. The dose in subjects who discontinued the study during maintenance phase II was 120 mg/day in 4 subjects and 160 mg/day in 2 subjects. Of 115 subjects who entered maintenance phase I, 110 subjects completed this phase and entered maintenance phase II. Of 110 subjects who entered maintenance phase II, 104 subjects (94.5%) completed this phase. The dose was maintained at 120 mg/day in 79 subjects, while it was increased to 160, 200, and 240 mg/day in 18, 8, and 5 subjects, respectively. The numbers of subjects who completed study drug treatment at

[55] Major inclusion criteria: Japanese patients with hyperuricaemia including gout; aged ≥20 and <75 years at the time of informed consent; serum uric acid level in the run-in period of ≥7.0 mg/dL in patients with tophi or a history of gout attacks or ≥9.0 mg/dL in patients with hyperuricaemia (≥8.0 mg/dL in patients receiving treatment for or with a diagnosis of urolithiasis, hypertension, hyperlipidemia, or diabetes). A washout period of ≥2 weeks was provided before the run-in period for subjects who had taken drugs that affect serum uric acid level (including drugs for gout and hyperuricaemia). Patients showing primary or secondary hyperuricaemia were excluded.

120, 160, and 200 mg/day were 75, 16, and 13, respectively.

The efficacy in terms of the primary endpoint, i.e. percentage decrease in serum uric acid level from baseline at the end of treatment in the FAS (mean ± SD [two-sided 95% CI]), was 38.44% ± 13.34% [36.04, 40.84].

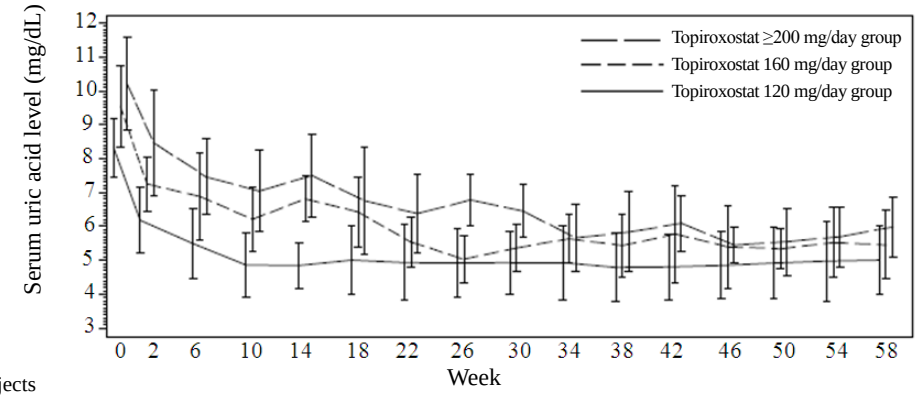
The secondary endpoint, i.e. percentage decrease in serum uric acid level from baseline by final dose level, is shown in Table 44.

Table 44. Percentage decrease in serum uric acid level from baseline at the end of treatment by final dose level (Study FY1002, FAS)

Final topiroxostat dose	Number of subjects	Percentage decrease in serum uric acid level (%)	Two-sided 95% CI	Median [minimum, maximum]
120 mg/day	84	38.60 ± 13.08	[35.76, 41.44]	40.78 [-1.2, 63.2]
160 mg/day	18	42.60 ± 12.51	[36.38, 48.83]	43.92 [24.4, 67.9]
≥ 200 mg/day	13	40.88 ± 8.89	[35.50, 46.25]	42.86 [25.5, 53.8]
< 120 mg/day	6	18.34 ± 12.00	[5.75, 30.94]	22.20 [-1.4, 30.5]

Mean ± SD

The time course of serum uric acid levels is shown in Figure 2.



Number of subjects																
Topiroxostat ≥200 mg/day group	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
Topiroxostat 160 mg/day group	18	18	18	18	18	18	18	18	18	17	17	16	16	16	16	16
Topiroxostat 120 mg/day group	84	84	83	82	81	79	79	78	76	77	75	75	75	76	75	74

Figure 2. Time course of serum uric acid levels from the start of treatment (Study FY1002, FAS, mean ± SD)

The percentage of subjects who achieved the target serum uric acid level of ≤6.0 mg/dL was 70.0% (77 of 110 subjects) at Week 18 (before dose increase) and 71.9% (87 of 121 subjects) at the end of treatment.

Safety results showed the following cumulative incidence at the end of treatment: 97.5% (118 of 121 subjects) for adverse events and 67.8% (82 of 121 subjects) for adverse drug reactions. The dose-specific incidence of adverse events at the end of treatment was 96.4% (81 of 84 subjects) in the 120 mg/day group, 100.0% (18 of 18 subjects) in the 160 mg/day group, 100.0% (13 of 13 subjects) in the ≥200 mg/day group, and 100.0% (6 of 6 subjects) in the <120 mg/day group. The incidence of adverse drug reactions was 66.7% (56 of 84 subjects) in the 120 mg/day group, 72.2% (13 of 18 subjects) in the 160 mg/day group, 53.8% (7 of 13 subjects) in the ≥200 mg/day group, and 100.0% (6

of 6 subjects) in the <120 mg/day group. The adverse events and/or adverse drug reactions reported in ≥5% of subjects in all topiroxostat groups are shown in Table 45.

Table 45. Adverse events and/or adverse drug reactions reported in ≥5% of subjects in all topiroxostat groups (Study FY1002, safety analysis set)

Name of event	All topiroxostat groups (n = 121)		Topiroxostat 120 mg/day group[a)] (n = 84)		Topiroxostat 160 mg/day group[a)] (n = 18)		Topiroxostat ≥200 mg/day group[a)] (n = 13)		Topiroxostat <120 mg/day group[a)] (n = 6)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
Any event	97.5 (118)	67.8 (82)	96.4 (81)	66.7 (56)	100.0 (18)	72.2 (13)	100.0 (13)	53.8 (7)	100.0 (6)	100.0 (6)
Nasopharyngitis	26.4 (32)	0.0 (0)	31.0 (26)	0.0 (0)	16.7 (3)	0.0 (0)	23.1 (3)	0.0 (0)	0.0 (0)	0.0 (0)
Upper respiratory tract inflammation	12.4 (15)	0.0 (0)	11.9 (10)	0.0 (0)	22.2 (4)	0.0 (0)	7.7 (1)	0.0 (0)	0.0 (0)	0.0 (0)
Back pain	8.3 (10)	0.0 (0)	10.7 (9)	0.0 (0)	0.0 (0)	0.0 (0)	7.7 (1)	0.0 (0)	0.0 (0)	0.0 (0)
Gout arthritis	9.1 (11)	4.1 (5)	9.5 (8)	4.8 (4)	5.6 (1)	0.0 (0)	15.4 (2)	7.7 (1)	0.0 (0)	0.0 (0)
Pain in extremity	5.8 (7)	0.8 (1)	2.4 (2)	0.0 (0)	16.7 (3)	0.0 (0)	15.4 (2)	7.7 (1)	0.0 (0)	0.0 (0)
ALT increased	27.3 (33)	13.2 (16)	27.4 (23)	14.3 (12)	38.9 (7)	16.7 (3)	15.4 (2)	0.0 (0)	16.7 (1)	16.7 (1)
Albumin urine present	10.7 (13)	6.6 (8)	10.7 (9)	6.0 (5)	11.1 (2)	11.1 (2)	0.0 (0)	0.0 (0)	33.3 (2)	16.7 (1)
α1 globulin increased	5.8 (7)	4.1 (5)	6.0 (5)	3.6 (3)	11.1 (2)	11.1 (2)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
AST increased	28.9 (35)	9.9 (12)	31.0 (26)	11.9 (10)	33.3 (6)	11.1 (2)	23.1 (3)	0.0 (0)	0.0 (0)	0.0 (0)
β2 microglobulin increased	16.5 (20)	11.6 (14)	19.0 (16)	14.3 (12)	11.1 (2)	5.6 (1)	15.4 (2)	7.7 (1)	0.0 (0)	0.0 (0)
β2 microglobulin urine increased	30.6 (37)	20.7 (25)	31.0 (26)	19.0 (16)	22.2 (4)	22.2 (4)	46.2 (6)	30.8 (4)	16.7 (1)	16.7 (1)
NAG increased	32.2 (39)	19.8 (24)	33.3 (28)	23.8 (20)	44.4 (8)	11.1 (2)	15.4 (2)	7.7 (1)	16.7 (1)	16.7 (1)
Blood amylase increased	5.8 (7)	3.3 (4)	7.1 (6)	4.8 (4)	0.0 (0)	0.0 (0)	7.7 (1)	0.0 (0)	0.0 (0)	0.0 (0)
Blood bilirubin increased	7.4 (9)	2.5 (3)	9.5 (8)	3.6 (3)	5.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Blood creatine phosphokinase increased	21.5 (26)	2.5 (3)	22.6 (19)	2.4 (2)	27.8 (5)	0.0 (0)	7.7 (1)	0.0 (0)	16.7 (1)	16.7 (1)
Blood creatinine increased	7.4 (9)	4.1 (5)	9.5 (8)	6.0 (5)	0.0 (0)	0.0 (0)	7.7 (1)	0.0 (0)	0.0 (0)	0.0 (0)
Blood lactate dehydrogenase increased	14.0 (17)	2.5 (3)	16.7 (14)	3.6 (3)	5.6 (1)	0.0 (0)	15.4 (2)	0.0 (0)	0.0 (0)	0.0 (0)
Blood triglycerides increased	38.8 (47)	7.4 (9)	42.9 (36)	7.1 (6)	38.9 (7)	5.6 (1)	30.8 (4)	15.4 (2)	0.0 (0)	0.0 (0)
C-reactive protein increased	9.9 (12)	0.0 (0)	10.7 (9)	0.0 (0)	5.6 (1)	0.0 (0)	7.7 (1)	0.0 (0)	16.7 (1)	0.0 (0)
γ-GTP increased	17.4 (21)	7.4 (9)	14.3 (12)	8.3 (7)	22.2 (4)	5.6 (1)	30.8 (4)	0.0 (0)	16.7 (1)	16.7 (1)
Glucose urine present	5.8 (7)	0.0 (0)	6.0 (5)	0.0 (0)	11.1 (2)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Blood urine present	14.0 (17)	2.5 (3)	15.5 (13)	3.6 (3)	11.1 (2)	0.0 (0)	15.4 (2)	0.0 (0)	0.0 (0)	0.0 (0)
Red blood cells urine positive	6.6 (8)	1.7 (2)	6.0 (5)	1.2 (1)	5.6 (1)	5.6 (1)	15.4 (2)	0.0 (0)	0.0 (0)	0.0 (0)
White blood cell count increased	14.9 (18)	0.8 (1)	10.7 (9)	0.0 (0)	27.8 (5)	0.0 (0)	30.8 (4)	7.7 (1)	0.0 (0)	0.0 (0)
Monocyte percentage increased	9.1 (11)	4.1 (5)	10.7 (9)	6.0 (5)	0.0 (0)	0.0 (0)	15.4 (2)	0.0 (0)	0.0 (0)	0.0 (0)
Protein urine present	7.4 (9)	2.5 (3)	8.3 (7)	3.6 (3)	11.1 (2)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
α1 microglobulin urine increased	37.2 (45)	27.3 (33)	35.7 (30)	25.0 (21)	50.0 (9)	44.4 (8)	30.8 (4)	15.4 (2)	33.3 (2)	33.3 (2)

% incidence (number of subjects with events), MedDRA/J (ver. 13.0)
a) Final dose level

One subject in the 160 mg/day group died (bile duct cancer), but a causal relationship with the study drug was ruled out. The following 8 other serious adverse events occurred in 9 subjects in the 120 mg/day group: "oesophageal carcinoma," "osteoarthritis," and "macular oedema" during maintenance phase I (120 mg/day); "aortic aneurysm/coronary artery stenosis," "diverticulitis," "calculus ureteric," and "inguinal hernia" during maintenance phase II; and "cardiac failure congestive" after treatment completion. "Aortic aneurysm," "coronary artery stenosis," and "cardiac failure congestive" were classified as adverse drug reactions. Adverse events leading to study discontinuation occurred in 11 subjects (20 events), including 1 subject (ALT increased/face oedema/feeling abnormal/malaise/thirst) during initial phase I (40 mg/day), 2 subjects (cheilitis/glossitis/oropharyngeal discomfort/rash, chills/cold sweat) during initial phase II (80 mg/day), 3 subjects (ALT increased, ALT increased/AST

increased, oesophageal carcinoma) during maintenance phase I (120 mg/day), 4 subjects (myelopathy, aortic aneurysm, diverticulitis, cardiac failure congestive [after treatment]) treated at 120 mg/day during maintenance phase II, and 1 subject (bile duct cancer [death]) treated at 160 mg/day during maintenance phase II.

The incidence of gout arthritis in each treatment phase is shown in Table 46.

Table 46. Incidence of gout arthritis by treatment time point (Study FY1002, safety analysis set)

Time point	All topiroxostat groups	Topiroxostat 120 mg/day group[a)]	Topiroxostat 160 mg/day group[a)]	Topiroxostat ≥200 mg/day group[a)]	Topiroxostat < 120 mg/day group[a)]
Initial phase I	2.5 (3/121)	3.6 (3/84)	0.0 (0/18)	0.0 (0/13)	0.0 (0/6)
Initial phase II	2.5 (3/118)	2.4 (2/84)	0.0 (0/18)	7.7 (1/13)	0.0 (0/3)
Week 4 in maintenance phase I	1.7 (2/115)	1.2 (1/84)	5.6 (1/18)	0.0 (0/13)	0.0 (0/0)
Week 8 in maintenance phase I	3.5 (4/113)	3.7 (3/82)	0.0 (0/18)	7.7 (1/13)	0.0 (0/0)
Week 12 in maintenance phase I	0.0 (0/111)	0.0 (0/80)	0.0 (0/18)	0.0 (0/13)	0.0 (0/0)
Week 4 in maintenance phase II	0.9 (1/110)	0.0 (0/79)	5.6 (1/18)	0.0 (0/13)	0.0 (0/0)
Week 8 in maintenance phase II	0.0 (0/109)	0.0 (0/78)	0.0 (0/18)	0.0 (0/13)	0.0 (0/0)
Week 12 in maintenance phase II	0.0 (0/109)	0.0 (0/78)	0.0 (0/18)	0.0 (0/13)	0.0 (0/0)
Week 16 in maintenance phase II	0.0 (0/108)	0.0 (0/77)	0.0 (0/18)	0.0 (0/13)	0.0 (0/0)
Week 20 in maintenance phase II	0.9 (1/106)	0.0 (0/76)	0.0 (0/17)	7.7 (1/13)	0.0 (0/0)
Week 24 in maintenance phase II	0.0 (0/105)	0.0 (0/76)	0.0 (0/16)	0.0 (0/13)	0.0 (0/0)
Week 28 in maintenance phase II	0.0 (0/105)	0.0 (0/76)	0.0 (0/16)	0.0 (0/13)	0.0 (0/0)
Week 32 in maintenance phase II	0.0 (0/105)	0.0 (0/76)	0.0 (0/16)	0.0 (0/13)	0.0 (0/0)
Week 36 in maintenance phase II	1.9 (2/105)	2.6 (2/76)	0.0 (0/16)	0.0 (0/13)	0.0 (0/0)
Week 40 in maintenance phase II	1.0 (1/105)	1.3 (1/76)	0.0 (0/16)	0.0 (0/13)	0.0 (0/0)
Week >40 in maintenance phase II	0.0 (0/104)	0.0 (0/75)	0.0 (0/16)	0.0 (0/13)	0.0 (0/0)
Entire period	9.10 (11/121)	9.50 (8/84)	5.60 (1/18)	15.4 (2/13)	0.0 (0/6)

% incidence (number of subjects with events/number of analyzed subjects)
a) Final dose level

Changes in vital signs and 12-lead ECG included abnormal changes in blood pressure[53] in 6 of 121 subjects (5.0%), but there were no clinically relevant changes in 12-lead ECG.

4.(iii).A.(3).4) Placebo-controlled study in patients with concurrent moderate renal impairment (Study FY1003, 5.3.5.1-7, [redacted] 20[redacted] to [redacted] 20[redacted])

A randomized, placebo-controlled, double-blind, parallel-group study was conducted in Japanese patients with hyperuricaemia including gout and concurrent moderate renal impairment[56] (target number of subjects, 120) to evaluate the efficacy and safety of topiroxostat.

[56] Major inclusion criteria: Japanese patients with hyperuricaemia including gout; aged ≥20 and <75 years at the time of informed consent; serum uric acid level in the run-in period of ≥7.0 mg/dL in patients with tophi or a history of gout attacks or ≥8.0 mg/dL in patients with hyperuricaemia; concurrent moderate renal impairment ($30 \leq$ eGFR < 60 mL/min/1.73 m^2) ≥8 weeks before the start of the run-in period and in the run-in period. A washout period of ≥2 weeks was provided before the run-in period for subjects who had taken drugs that affect serum uric acid level (including drugs for gout and hyperuricaemia). Patients showing primary or secondary hyperuricaemia were excluded.
eGFR was calculated from serum creatinine level (Scr) using the formula: eGFR = $194 \times Scr^{-1.094} \times age^{-0.287}$ for males; eGFR = $0.739 \times 194 \times Scr^{-1.094} \times age^{-0.287}$ for females.

This study consisted of a run-in period (8 weeks) and a treatment period (initial phase I, 2 weeks; initial phase II, 4 weeks; maintenance phase I, 8 weeks; maintenance phase II, 8 weeks).

The placebo group received the placebo orally twice daily after the morning and evening meals throughout the treatment period. The topiroxostat group received topiroxostat orally twice daily after the morning and evening meals at 20 mg/dose (40 mg/day) during the 2 weeks of initial phase I, 40 mg/dose (80 mg/day) during the 4 weeks of initial phase II, 60 mg/dose (120 mg/day) during the 8 weeks of maintenance phase I, and 80 mg mg/dose (160 mg/day) during the 8 weeks of maintenance phase II.[57]

All 122 treated subjects (62 subjects in the topiroxostat group and 60 subjects in the placebo group) were included in the safety analysis set and the FAS, and the FAS was defined as the efficacy analysis set. The study was discontinued in: 1 subject (adverse events) in the topiroxostat group during initial phase I; 2 subjects (consent withdrawal) in the placebo group and 1 subject (consent withdrawal) in the topiroxostat group during initial phase II; 3 subjects (consent withdrawal, 2 subjects; adverse events, 1 subject) in the placebo group and 2 subjects (consent withdrawal, adverse events) in the topiroxostat group during maintenance phase I; and 2 subjects (adverse events) in the topiroxostat group during maintenance phase II.

Two primary endpoints (percentage decrease in serum uric acid level and change in eGFR, both from baseline, at the end of treatment) were used for efficacy evaluation. The change in eGFR was compared between the topiroxostat group and the placebo group when a statistically significant difference was detected in the percentage decrease in serum uric acid level between the two groups. The percentage decrease in serum uric acid level from baseline at the end of study drug treatment in the FAS, one of the primary endpoints shown in Table 47, demonstrated a statistically significant difference between the topiroxostat group and the placebo group ($P < 0.0001$, t-test with a two-sided significance level of 5%). The change in eGFR from baseline at the end of study drug treatment, the other primary endpoint shown in Table 48, showed no statistically significant difference between the topiroxostat group and the placebo group ($P = 0.2240$, t-test with a two-sided significance level of 5%).

[57] When gout arthritis that occurred during the treatment period did not resolve at Weeks 2, 6 or 14 the same dose was allowed to be continued without dose escalation until resolution of the gout arthritis, for a maximum of 1 additional week from the day specified for each time point (until Day 22 for the occurrence at Week 2, until Day 50 for the occurrence at Week 6 and until Day 106 for the occurrence at Week 14). The study was discontinued when gout arthritis did not resolve within a maximum of 1 week. When gout arthritis was noted at Week 22 (the last day of treatment), study drug administration was continued further for a maximum of 1 additional week (until Day 162), in principle until resolution of gout arthritis, and the study was discontinued when gout arthritis did not resolve within a maximum of 1 week.

Table 47. Percentage decrease in serum uric acid level from baseline at the end of treatment (Study FY1003, FAS)

Treatment group	Baseline serum uric acid level (mg/dL)	Serum uric acid level at the end of study drug treatment (mg/dL)	Percentage decrease in serum uric acid level from baseline at the end of study drug treatment (%)	Between-group difference and two-sided 95% CI	*P*-value[b)]
Placebo group (n = 60)	8.47 ± 1.28	8.44 ± 1.31	-0.08 ± 9.92	–	–
Topiroxostat group (n = 62)	8.47 ± 1.24	4.51 ± 1.52 [a)]	45.38 ± 21.80[a)]	45.46 [39.33, 51.58][a)]	*P* < 0.0001 [a)]

Mean ± SD; –, not applicable

a) Two discontinued subjects were excluded from analysis because the serum uric acid level at the end of treatment met the exclusion criteria ("deviation of timing" and/or "because blood was collected ≥24 hours after administration") when the measurements at the end of treatment were evaluated. Topiroxostat group, 60 subjects.

b) t-test, two-sided 5% significance level

Table 48. Change in eGFR from baseline at the end of treatment (Study FY1003, FAS)

Treatment group	Baseline eGFR	eGFR at the end of study drug treatment	Change in eGFR from baseline at the end of study drug treatment	Between-group difference and two-sided 95% CI	*P*-value[a)]
Placebo group (n = 60)	48.89 ± 8.51	48.44 ± 8.38	-0.45 ± 4.72	1.08 [-0.67, 2.83]	*P* = 0.2240
Topiroxostat group (n = 62)	49.40 ± 8.93	50.03 ± 9.81	0.63 ± 5.03		

Mean ± SD; unit, mL/min/1.73m^2

a) t-test with a two-sided significance level of 5%, conducted when the other primary endpoint, the percentage decrease in serum uric acid level from baseline at the end of treatment, showed a statistically significant difference between the topiroxostat group and the placebo group.

Safety results showed the following cumulative incidence of adverse events at the end of treatment: 68.3% (41 of 60 subjects) in the placebo group and 67.7% (42 of 62 subjects) in the topiroxostat group. The incidence of adverse drug reactions was 23.3% (14 of 60 subjects) in the placebo group and 40.3% (25 of 62 subjects) in the topiroxostat group. The adverse events and/or adverse drug reactions reported in ≥5% of subjects in any treatment group are shown in Table 49.

Table 49. Adverse events and/or adverse drug reactions reported in ≥5% of subjects in any treatment group (Study FY1003, safety analysis set)

Name of event	Placebo group (n = 60)		Topiroxostat group (n = 62)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
Any event	68.3 (41)	23.3 (14)	67.7 (42)	40.3 (25)
Nasopharyngitis	21.7 (13)	0.0 (0)	21.0 (13)	0.0 (0)
Conjunctivitis allergic	6.7 (4)	0.0 (0)	1.6 (1)	0.0 (0)
Rhinitis allergic	6.7 (4)	0.0 (0)	1.6 (1)	0.0 (0)
Upper respiratory tract inflammation	6.7 (4)	0.0 (0)	0.0 (0)	0.0 (0)
Diarrhoea	5.0 (3)	3.3 (2)	1.6 (1)	0.0 (0)
Arthralgia	1.7 (1)	1.7 (1)	9.7 (6)	3.2 (2)
Gout arthritis	8.3 (5)	6.7 (4)	14.5 (9)	14.5 (9)
ALT increased	0.0 (0)	0.0 (0)	12.9 (8)	9.7 (6)
Albumin urine present	5.0 (3)	5.0 (3)	0.0 (0)	0.0 (0)
AST increased	3.3 (2)	3.3 (2)	9.7 (6)	8.1 (5)

% incidence (number of subjects with events), MedDRA/J (ver.13.0)

No deaths occurred. Serious adverse events included 2 events (hypoglycaemia, hepatitis acute) in 2 subjects of the placebo group and 4 events (polyarthritis/circulatory collapse, contusion/cerebral haemorrhage) in 2 subjects of the topiroxostat group, and "polyarthritis" and "hepatitis acute" were classified as adverse drug reactions. Adverse events leading to study discontinuation included "hepatitis acute" in 1 subject of the placebo group and 4 events (ALT increased/AST increased, eczema, polyarthritis) in 3 subjects of the topiroxostat group.

The incidence of gout arthritis in each treatment phase is shown in Table 50.

Table 50. Incidence of gout arthritis by treatment time point (Study FY1003, safety analysis set)

Time point	Placebo group	Topiroxostat group
Initial phase I	3.3 (2/60)	1.6 (1/62)
Initial phase II	1.7 (1/60)	0.0 (0/61)
Week 4 in maintenance phase I	0.0 (0/58)	1.7 (1/60)
Week 8 in maintenance phase I	1.8 (1/56)	3.3 (2/60)
Week 4 in maintenance phase II	1.8 (1/55)	6.9 (4/58)
Week 8 in maintenance phase II	1.8 (1/55)	3.5 (2/57)
Week >8 in maintenance phase II	0.0 (0/55)	0.0 (0/56)
All phases	8.3 (5/60)	14.5 (9/62)

% incidence (number of subjects with events/number of analyzed subjects)

Changes in vital signs and 12-lead ECG included abnormal changes in blood pressure[53] in 2 of 60 subjects (3.3%) in the placebo group and 2 of 62 subjects (3.2%) in the topiroxostat group, but there were no clinically relevant changes in 12-lead ECG.

4.(iii).B Outline of the review by PMDA

4.(iii).B.(1) Clinical positioning

PMDA considers as follows:

Other uric acid production inhibitors (drugs in the same class as topiroxostat, XOR inhibitors) available in Japan include allopurinol and febuxostat. Allopurinol has been in clinical use for more than 40 years, but adequate caution and appropriate measures are required when this drug is used in patients with renal impairment, and the dose needs to be reduced depending on the level of renal function. Febuxostat has recently become clinically available in Japan as a novel XOR inhibitor that requires no dose reduction depending on renal function. Given that the efficacy of topiroxostat was confirmed by clinical study results [see "4.(iii).B.(2) Efficacy"], that the safety is acceptable [see "4.(iii).B.(3) Safety"], and that dose reduction depending on the level of renal function is not considered to be necessary [see "4.(iii).B.(6).1) Patients with renal impairment" in "4.(iii).B.(6) Special populations"], topiroxostat can serve as a new treatment option.

4.(iii).B.(2) Efficacy

The applicant explained as follows:

A Japanese phase III study (Study FY1001) showed that the percentage decrease in serum uric acid level was similar between 120 mg/day of topiroxostat and 200 mg/day of allopurinol (Table 37), and that 72.4% of subjects (71 of 98 subjects) with hyperuricaemia including gout achieved the therapeutic goal (serum uric acid level of ≤6.0 mg/dL) (Table 39). The pooled long-term treatment study analysis[19] confirmed persistence of serum uric acid-lowering effect in topiroxostat subjects at 120 mg/day (Figure 3). Persistence of serum uric acid-lowering effect at an increased dose was also demonstrated in subjects who failed to achieve the target serum uric acid level of ≤6.0 mg/dL when treated at 120 mg/day, and had their dose increased to 160 mg/day (topiroxostat subjects at 160 mg/day, Figure 3).

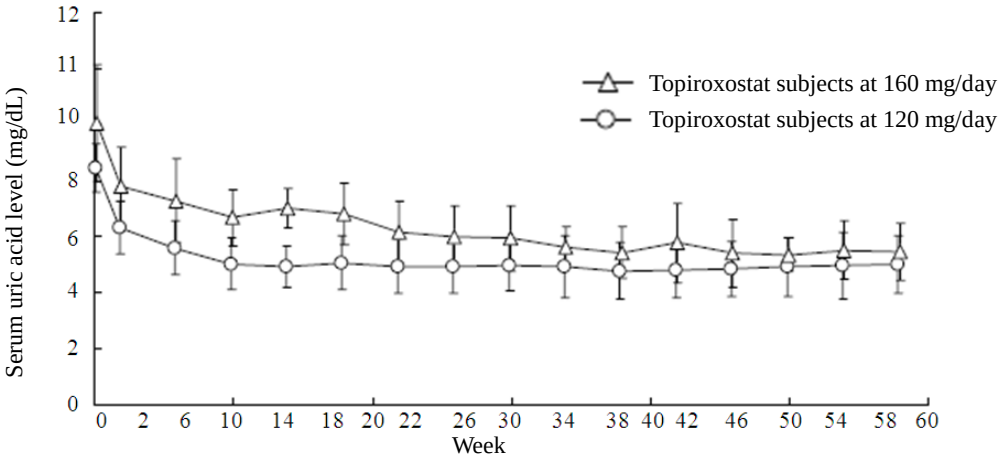


Figure 3. Time course of serum uric acid levels from the start of treatment (pooled long-term treatment study analysis, FAS, mean ± SD)

The effect of different clinical diagnoses (gout vs. hyperuricaemia) on efficacy was analyzed in the pooled double-blind study analysis[10]. Table 51 shows the following results: the percentage decrease and the extent of change in the serum uric acid level from baseline at the end of the double-blind period and the percentage of subjects who achieved the target serum uric acid level of ≤6.0 mg/dL at the end of double-blind period. Although the baseline serum uric acid level differed slightly between subjects with "gout" and those with "sole hyperuricaemia," the difference in clinical diagnosis (gout vs. hyperuricaemia) was not reflected in major differences in the serum uric acid-lowering effect of topiroxostat.

Table 51. Percentage decrease in serum uric acid level and percentage of subjects achieving a serum uric acid level of ≤6.0 mg/dL in the pooled double-blind study analysis[a)] (FAS, LOCF)

	Placebo group		Topiroxostat 120 mg/day group		Topiroxostat 160 mg/day group	
	Gout (n = 92)	Hyperuricaemia only (n = 43)	Gout (n = 151)	Hyperuricaemia only (n = 48)	Gout (n = 85)	Hyperuricaemia only (n = 39)
Baseline serum uric acid level (mg/dL)	8.85 ± 1.28	8.69 ± 1.01	8.96 ± 1.28	8.80 ± 0.74	8.90 ± 1.46	8.71 ± 0.99
Percentage decrease from baseline at the end of double-blind period (%)	0.68 ± 11.45	0.87 ± 9.59	35.65 ± 12.67	36.48 ± 13.48	43.80 ± 19.71	48.43 ± 10.21
Amount of change from baseline at the end of double-blind period (mg/dL)	-0.10 ± 1.02	-0.11 ± 0.88	-3.20 ± 1.23	-3.23 ± 1.26	-3.96 ± 1.76	-4.22 ± 0.97
Percentage of subjects achieving a serum uric acid level of ≤6.0 mg/dL at the end of double-blind period (%) [95% CI]	0.0 [0.0, 3.9]	0.0 [0.0, 8.2]	61.6 [53.3, 69.4]	75.0 [60.4, 86.4]	77.6 [67.3, 86.0]	94.9 [82.7, 99.4]

a) In Studies FYX-051-221 and FYX-051-222, topiroxostat was administered at 40 mg/day for 2 weeks, followed by treatment at 120 mg/day or 160 mg/day. In Study FYX-051-323, topiroxostat was administered at 40 mg/day for 2 weeks, and then at 80 mg/day for 4 weeks, followed by treatment at 120 mg/day or 160 mg/day. In Study FY1001, topiroxostat was administered at 40 mg/day for 2 weeks, and then at 80 mg/day for 4 weeks, followed by treatment at 120 mg/day. In FY1003 Study, topiroxostat was administered at 40 mg/day for 2 weeks, and then at 80 mg/day for 4 weeks, followed by 8-week treatment at 120 mg/day and subsequent 8-week forced-dose-escalation treatment at 160 mg/day.

PMDA considers as follows:

The efficacy of topiroxostat has been demonstrated based on the following results: the primary endpoints of the phase III study (Study FY1001, Table 37), the time course of serum uric acid levels in the pooled long-term treatment study analysis (Figure 3), and the assessment of efficacy specific to

clinical diagnosis (gout vs. hyperuricaemia, Table 51). Given that febuxostat had not been approved when the phase III study (Study FY1001) was started (20[redacted]), it was appropriate that allopurinol, a drug in the same class (uric acid production inhibitors [XOR inhibitors]) as topiroxostat, was selected as the comparator for this study.

4.(iii).B.(3) Safety

The applicant explained as follows:

The incidence of adverse events and adverse drug reactions in the pooled double-blind study analysis[10] is shown in Table 52. The incidence of adverse events in the topiroxostat group (all doses pooled) and those at maintenance-phase dose groups (including subjects who were assigned to the 120 mg/day group or 160 mg/day group and received ≥1 doses of topiroxostat) did not differ significantly in comparison with the placebo or allopurinol group. The incidence of adverse drug reactions also did not differ significantly between these treatment groups. The incidence, specific to topiroxostat dose, of adverse events and adverse drug reactions during the maintenance phase was 73.3% (55 of 75 subjects) and 32.0% (24 of 75 subjects), respectively, in the ≤60 mg/day groups, 66.1% (41 of 62 subjects) and 29.0% (18 of 62 subjects), respectively, in the 80 mg/day group, 80.1% (161 of 201 subjects) and 30.8% (62 of 201 subjects), respectively, in the 120 mg/day group, and 68.5% (87 of 127 subjects) and 33.1% (42 of 127 subjects), respectively, in the 160 mg/day group, and thus indicated no trend of dose-dependent increase in incidence. Furthermore, the incidence of study discontinuation due to adverse events or adverse drug reactions did not tend to increase with dose.

Table 52. Incidence of adverse events and adverse drug reactions in the pooled double-blind study analysis

	Placebo group (n = 135)	Topiroxostat group (all doses pooled) (n = 465)	Topiroxostat maintenance-phase dose group (n = 328)	Allopurinol group (n = 144)
Any adverse event	71.9 (97)	74.0 (344)	75.6 (248)	84.0 (121)
	2.434 (5.822)[a)]	2.982 (8.582)[a)]	2.669 (8.676)[a)]	2.902 (10.384)[a)]
Serious adverse events (including death)	2.2 (3)	1.1 (5)	1.5 (5)	1.4 (2)
Death due to adverse event	0.0 (0)	0.0 (0)	0.0 (0)	1.4 (2)
Discontinuation due to adverse event	4.4 (6)	2.6 (12)	3.0 (10)	4.9 (7)
Discontinuation due to serious adverse event	1.5 (2)	0.4 (2)	0.6 (2)	1.4 (2)
Any adverse drug reaction	29.6 (40)	31.4 (146)	31.7 (104)	27.1 (39)
	1.004 (1.506)[a)]	1.266 (2.358)[a)]	1.119 (2.185)[a)]	0.935 (1.727)[a)]
Serious adverse drug reactions (including death)	0.7 (1)	0.2 (1)	0.3 (1)	0.0 (0)
Death due to adverse drug reaction	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Discontinuation due to adverse drug reaction	3.7 (5)	2.6 (12)	3.0 (10)	2.1 (3)
Discontinuation due to serious adverse drug reaction	0.7 (1)	0.2 (1)	0.3 (1)	0.0 (0)

% incidence (number of subjects with events)
Topiroxostat group (all doses pooled): Includes all subjects who received ≥1 doses of topiroxostat regardless of dose.
Topiroxostat maintenance-phase dose group: Includes all subjects whose final topiroxostat dose was 120 or 160 mg/day.
a) Incidence rate based on the number of subjects per subjects-year (Incidence rate based on the number of events per subject-year)

The incidence of adverse events and adverse drug reactions from the pooled long-term treatment study analysis[19] is shown in Table 53. These results indicate that there were no major differences between the topiroxostat group (all doses pooled) and the topiroxostat maintenance-phase dose group.

Table 53. Incidence of adverse events and adverse drug reactions in the pooled long-term treatment study analysis

	Topiroxostat group (all doses pooled) (n = 361)	Topiroxostat maintenance-phase dose group (n = 348)
Any adverse event	88.9 (321)	88.5 (308)
Serious adverse events (including death)	5.0 (18)	5.2 (18)
Death due to adverse event	0.3 (1)	0.3 (1)
Discontinuation due to adverse event	7.5 (27)	7.8 (27)
Discontinuation due to serious adverse event	3.0 (11)	3.2 (11)
Adverse drug reactions	40.4 (146)	39.9 (139)
Serious adverse drug reactions (including death)	1.4 (5)	1.4 (5)
Death due to adverse drug reaction	0.0 (0)	0.0 (0)
Discontinuation due to adverse drug reaction	3.9 (14)	4.0 (14)
Discontinuation due to serious adverse drug reaction	0.8 (3)	0.9 (3)

% incidence (number of subjects with events)
Topiroxostat group (all doses pooled): Included all subjects who received ≥1 doses of topiroxostat regardless of dose.
Topiroxostat maintenance-phase dose group: Included all subjects whose final topiroxostat dose was ≤160 mg/day.

The same pooled analysis showed the incidence of initial adverse events and adverse drug reactions in each treatment phase (Table 54). These also indicated that there were no major differences between treatment phases. The incidence of discontinuation due to adverse events or adverse drug reactions decreased after the third month of the maintenance phase.

Table 54. Incidence of initial adverse events and adverse drug reactions in each treatment phase in the pooled long-term treatment study analysis

	Total of topiroxostat group (all doses pooled) (n = 361)	Initial phase (6 weeks) (n = 361)	Before 3rd month of maintenance phase (n = 345)	3rd to 6th month of maintenance phase (n = 330)	6th to 9th month of maintenance phase (n = 166)	9th to 12th month of maintenance phase (n = 105)	After 12th month of maintenance phase (n = 105)
Any adverse event	88.9 (321)	55.7 (201)	58.6 (202)	53.0 (175)	42.8 (71)	47.6 (50)	21.9 (23)
Death due to adverse event	0.3 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.6 (1)	0.0 (0)	0.0 (0)
Serious adverse events excluding death	4.7 (17)	0.3 (1)	2.6 (9)	1.2 (4)	1.2 (2)	0.0 (0)	1.0 (1)
Discontinuation due to adverse event	7.5 (27)	2.8 (10)	3.2 (11)	0.9 (3)	1.2 (2)	0.0 (0)	1.0 (1)
Any adverse drug reaction	40.4 (146)	20.2 (73)	17.4 (60)	12.4 (41)	12.0 (20)	17.1 (18)	11.4 (12)
Death due to adverse drug reaction	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Serious adverse drug reactions excluding death	1.4 (5)	0.0 (0)	0.6 (2)	0.6 (2)	0.6 (1)	0.0 (0)	0.0 (0)
Discontinuation due to adverse drug reaction	3.9 (14)	1.9 (7)	1.4 (5)	0.3 (1)	0.6 (1)	0.0 (0)	0.0 (0)

% incidence (number of subjects with events)

PMDA considers that the safety of topiroxostat is at present acceptable based on the results from the pooled double-blind study analysis and the pooled long-term treatment study analysis. Individual adverse events including gout arthritis, liver disorder, and adverse events related to the kidney or bladder will be further discussed in 4.(iii).B.(3).1) to 4) below.

4.(iii).B.(3).1) Gout arthritis

The applicant explained as follows:

A rapid drop in serum uric acid level by antihyperuricemic treatment is known to cause gout arthritis, resulting from inflammatory responses due to neutrophil phagocytosis of urate crystals released from the joint into synovial fluid (Shimizu T, *Modern Physician*. 2004;24:1394-6). Taking this into account, the "Guideline for the management of hyperuricaemia and gout, second edition" (edited by the Guideline Revision Committee of the Japanese Society of Gout and Nucleic Acid Metabolism, 2010;

hereinafter, referred to as the "Japanese guideline") recommends that, in medical treatment of hyperuricaemia, the serum uric acid level be gradually lowered to ≤6.0 mg/dL over a period of 3 to 6 months, and thereafter be maintained at ≤6.0 mg/dL. During the development of topiroxostat, gout arthritis occurring between the start and end of treatment or the discontinuation of study drug was evaluated by the investigator (sub-investigator) based on the "Diagnostic criteria for gout arthritis."[58] The incidence of gout arthritis in the phase II exploratory studies using a 1-step dose escalation procedure (Studies FYX-051-221 and FYX-051-222) and subsequent studies using a 2-step dose escalation procedure (Studies FYX-051-323, FY1001, and FY1003) is shown in Table 55. The incidence of gout arthritis was lower in the studies using a 2-step dose escalation procedure.

Table 55. Incidence of gout arthritis in the pooled double-blind study analysis

Dose escalation in initial phase		Switch to maintenance dose in 1 step after 2 weeks		Switch to maintenance dose in 2 steps (2 weeks in initial phase I, 4 weeks in initial phase II) after 6 weeks		
Study number (overall treatment period)		FYX-051-221[b] (8 weeks)	FYX-051-222[c] (12 weeks)	FYX-051-323[d] (16 weeks)	FY1001[e] (16 weeks)	FY1003[f] (22 weeks)
Placebo group		5.6 (2/36)	-	7.7 (3/39)	-	8.3 (5/60)
Topiroxostat group	40 mg/day group[a]	2.6 (1/38)	-	-	-	-
	60 mg/day group[a]	2.7 (1/37)	-	-	-	-
	80 mg/day group[a]	13.2 (5/38)	16.7 (4/24)	-	-	-
	120 mg/day group[a]	16.2 (6/37)	12.0 (3/25)	5.1 (2/39)	12.0 (12/100)	-
	160 mg/day group[a]	-	20.0 (5/25)	5.0 (2/40)	-	14.5 (9/62)
Allopurinol group		-	-	10.3 (4/39)	7.6 (8/105)	-

% incidence (number of subjects with events/number of analyzed subjects); –, not applicable

a) Dose level at the end of treatment

b) After placebo, 20 mg/day or 40 mg/day of topiroxostat was administered for 2 weeks in the initial phase, and the subjects entered the maintenance phase and received placebo, or 40 mg/day, 60 mg/day, 80 mg/day, or 120 mg/day of topiroxostat for 6 weeks.

c) After 40 mg/day of topiroxostat was administered for 2 weeks in the initial phase, the subjects entered the maintenance phase and received 80 mg/day, 120 mg/day, or 160 mg/day of topiroxostat for 10 weeks.

d) After placebo, 40 mg/day of topiroxostat or 100 mg/day of allopurinol was administered for 2 weeks in initial phase I, placebo, 80 mg/day of topiroxostat, or 200 mg/day of allopurinol was administered for 4 weeks in initial phase II. Then, the subjects entered the maintenance phase and received placebo, 120 mg/day or 160 mg/day of topiroxostat, or 200 mg/day of allopurinol for 10 weeks.

e) After 40 mg/day of topiroxostat or 100 mg/day of allopurinol was administered for 2 weeks in initial phase I, 80 mg/day of topiroxostat or 200 mg/day of allopurinol was administered for 4 weeks in initial phase II. Then, the subjects entered the maintenance phase and received 120 mg/day of topiroxostat or 200 mg/day of allopurinol for 10 weeks.

f) Placebo was administered in the placebo group for 22 weeks. In the topiroxostat group, after 40 mg/day of topiroxostat was administered for 2 weeks in initial phase I, 80 mg/day of topiroxostat was administered for 4 weeks in initial phase II. Then, the subjects entered the maintenance phase and received 120 mg/day of topiroxostat for 8 weeks in maintenance phase I, followed by treatment with 160 mg/day of topiroxostat for 8 weeks in maintenance phase II.

In the long-term treatment studies (Studies FYX-051-332 and FY1002), in which the dose was escalated in 2 steps and was increased if the effect was insufficient at the dose in maintenance phase I, the incidence of gout arthritis did not increase when the dose was increased from 120 mg/day to 160 mg/day (Table 56).

[58] A subject is considered to have gout arthritis if (1), (2), or (3) below is met
(1) Uric acid crystal is present in synovial fluid, (2) proven gouty tophus, (3) 5 of the following 10 items, a) to j), are met: a) history ≥2 episodes of acute arthritis; b) inflammation reaching the peak level within 24 hours; c) monoarthritis; d) joint redness; e) pain or swelling of the first metatarsophalangeal joint; f) unilateral lesion of the first metatarsophalangeal joint; g) unilateral lesion of the foot joint; h) gouty tophus (definitive or suspected diagnosis); i) asymmetric swelling on X-ray images; j) complete remission of attack.

Table 56. Incidence of gout arthritis in each treatment phase in long-term treatment studies (maintenance phase only)

Study number (overall treatment period)	Final topiroxostat dose	Initial phase I	Initial phase II	Maintenance phase I	Maintenance phase II			
		2 weeks	4 weeks	12 weeks	12 weeks	12 weeks	12 weeks	4 weeks
FYX-051-332 (30 weeks)	120 mg/day	3.5 (6/173)	2.9 (5/173)	5.2 (9/173)	2.5 (4/163)	–	–	–
	160 mg/day	1.7 (1/58)	3.4 (2/58)	8.6 (5/58)	6.9 (4/58)	–	–	–
FY1002 (58 weeks)	120 mg/day	3.6 (3/84)	2.4 (2/84)	4.8 (4/84)	0.0 (0/79)	0.0 (0/77)	2.6 (2/76)	1.3 (1/76)
	160 mg/day	0.0 (0/18)	0.0 (0/18)	5.6 (1/18)	5.6 (1/18)	0.0 (0/18)	0.0 (0/16)	0.0 (0/16)

% incidence (number of subjects with events/number of analyzed subjects); –, not applicable

Based on the above, a 2-step dose escalation procedure will be advised in the "Precautions for dosage and administration" section of the proposed package insert to caution about the occurrence of gout arthritis during the early treatment phase.

PMDA considers as follows:

There is no problem in the applicant's explanation that, based on the clinical study results, a 2-step dose escalation procedure has been adopted for topiroxostat, and the fact will be advised in order to reduce the incidence of gout arthritis during the early treatment phase [see "4.(iii).B.(5) Dosage and administration"]. It is important to reduce the incidence of gout arthritis in the treatment of gout and hyperuricaemia, and collection of information on the incidence of gout arthritis needs to be continued in the post-marketing surveillance.

4.(iii).B.(3).2) Hepatic impairment

The applicant explained as follows:

The incidence of major hepatic adverse events from the pooled double-blind study analysis[10] is shown in Table 57. This shows that the incidence of adverse events in the SOC "hepatobiliary disorders" was similar between the topiroxostat group (all doses pooled) and placebo group. A causal relationship with the study drug was ruled out for all events in the topiroxostat group (all doses pooled). The incidence of major liver-related laboratory adverse events was higher in the topiroxostat group (all doses pooled) than in the placebo and allopurinol groups, while the severity of all events was mild.

Table 57. Incidence of major hepatic adverse events in the pooled double-blind study analysis

	Placebo group (n = 135)	Topiroxostat group (all doses pooled) (n = 465)	Allopurinol group (n = 144)	Topiroxostat maintenance-phase dose group (n = 328)	Breakdown of topiroxostat group by maintenance-phase dose	
					Topiroxostat 120 mg/day (n = 201)	Topiroxostat 160 mg/day (n = 127)
SOC "Hepatobiliary disorders"	0.7 (1)	0.6 (3)	0.0 (0)	0.9 (3)	0.5 (1)	1.6 (2)
Cholelithiasis	0.0 (0)	0.2 (1)	0.0 (0)	0.3 (1)	0.5 (1)	0.0 (0)
Hepatic cyst	0.0 (0)	0.4 (2)	0.0 (0)	0.6 (2)	0.0 (0)	1.6 (2)
Hepatic steatosis	0.0 (0)	0.2 (1)	0.0 (0)	0.3 (1)	0.0 (0)	0.8 (1)
Hepatitis acute	0.7 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
ALT increased	4.4 (6)	12.5 (58)	8.3 (12)	13.7 (45)	15.4 (31)	11.0 (14)
AST increased	3.7 (5)	11.6 (54)	10.4 (15)	13.4 (44)	14.4 (29)	11.8 (15)
Blood bilirubin increased	0.7 (1)	1.9 (9)	2.8 (4)	1.5 (5)	2.0 (4)	0.8 (1)
γ-GTP increased	4.4 (6)	7.5 (35)	4.9 (7)	7.6 (25)	9.0 (18)	5.5 (7)
Blood alkaline phosphatase increased	0.7 (1)	1.7 (8)	0.7 (1)	1.8 (6)	2.0 (4)	1.6 (2)

% incidence (number of subjects with events), MedDRA/J (ver.14.1)

The incidence of major hepatic adverse events in each treatment phase from the pooled long-term treatment study analysis[19] is shown in Table 58. Among adverse events in the SOC "Hepatobiliary disorders," "cholelithiasis" and "hepatic steatosis" occurred frequently, but the adverse events classified as adverse drug reactions were limited to 1 case each of "cholelithiasis" at 120 mg/day, "hepatic function abnormal" at 160 mg/day, and "liver disorder" at 120 mg/day. The severity of 1 case each of "cholecystitis" and "liver disorder" at 120 mg/day in Study FYX-051-332 was moderate, but other events were mild. Among adverse events related to hepatic laboratory values observed in the topiroxostat group (all doses pooled), severity was moderate for 1 case of "ALT increased/AST increased" (the same subject and event as the above "liver disorder") at 120 mg/day in Study FYX-051-332, but other events were mild. Serious adverse events classified as adverse drug reactions were "liver disorder" (1 case) and "ALT increased/AST increased" (1 case) at 120 mg/day and 160 mg/day of topiroxostat, respectively, in Study FYX-051-332. The subject who experienced "liver disorder" had a high γ-GTP level during the run-in period, but ALT and AST were within the normal ranges. On Day 113, increases in ALT and AST accompanied by malaise revealed the onset of "liver disorder" (diagnosed as drug-induced liver disorder). The subject who experienced "ALT increased/AST increased" had a high γ-GTP level during the run-in period, but ALT and AST were within the normal ranges. Although ALT and AST increased after Day 63, the study drug continued to be administered, and serious "ALT increased/AST increased" occurred at Week 30.

The time course showed no increase in the incidence of "ALT increased" and "γ-GTP increased" over the course of treatment, and the incidence remained high until it began to decrease after the sixth month of the maintenance phase, while the incidence of "AST increased" remained at similar levels before and after the sixth month of the maintenance phase. The incidence of "blood bilirubin increased" and "blood alkaline phosphatase increased" did not differ significantly between treatment phases.

Table 58. Incidence of initial adverse events associated with major hepatic adverse events in each treatment phase in the pooled long-term treatment study analysis

	Total of topiroxostat group (all doses pooled) (n = 361)	Initial phase (6 weeks) (n = 361)	Before 3rd month of maintenance phase (n = 345)	3rd to 6th month of maintenance phase (n = 330)	6th to 9th month of maintenance phase (n = 166)	9th to 12th month of maintenance phase (n = 105)	After 12th month of maintenance phase (n = 105)
SOC "Hepatobiliary disorders"	4.4 (16)	0.3 (1)	0.9 (3)	1.8 (6)	2.4 (4)	1.9 (2)	1.0 (1)
Alcoholic liver disease	0.3 (1)	0.0 (0)	0.0 (0)	0.3 (1)	0.0 (0)	0.0 (0)	0.0 (0)
Cholecystitis	0.3 (1)	0.0 (0)	0.0 (0)	0.3 (1)	0.0 (0)	0.0 (0)	0.0 (0)
Cholelithiasis	1.1 (4)	0.0 (0)	0.3 (1)	0.3 (1)	0.6 (1)	1.0 (1)	0.0 (0)
Hepatic cyst	0.6 (2)	0.0 (0)	0.0 (0)	0.3 (1)	0.0 (0)	0.0 (0)	1.0 (1)
Hepatic function abnormal	0.6 (2)	0.3 (1)	0.3 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Hepatic steatosis	2.2 (8)	0.0 (0)	0.3 (1)	0.9 (3)	1.8 (3)	1.0 (1)	0.0 (0)
Liver disorder	0.3 (1)	0.0 (0)	0.3 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Gallbladder polyp	0.6 (2)	0.0 (0)	0.3 (1)	0.0 (0)	0.0 (0)	1.0 (1)	0.0 (0)
ALT increased	22.7 (82)	7.8 (28)	7.8 (27)	6.7 (22)	1.2 (2)	1.0 (1)	1.9 (2)
AST increased	18.3 (66)	2.5 (9)	5.2 (18)	7.9 (26)	4.2 (7)	4.8 (5)	1.0 (1)
Blood bilirubin increased	2.8 (10)	0.8 (3)	0.9 (3)	0.3 (1)	0.6 (1)	1.0 (1)	1.0 (1)
γ-GTP increased	11.4 (41)	3.0 (11)	4.1 (14)	3.6 (12)	1.2 (2)	1.9 (2)	0.0 (0)
Blood alkaline phosphatase increased	1.1 (4)	0.0 (0)	0.3 (1)	0.6 (2)	0.0 (0)	0.0 (0)	1.0 (1)

% incidence (number of subjects with events), MedDRA/J (ver.14.1)

The pooled double-blind study analysis showed that the percentage of subjects who had transaminase

levels of ≥3 times the upper limit of normal after the start of treatment was similar between the placebo group and topiroxostat group (all doses pooled): 1.5% (2 of 135 subjects) and 1.1% (5 of 465 subjects), respectively, for ALT and 1.5% (2 of 135 subjects) and 0.9% (4 of 465 subjects), respectively, for AST.

The pooled long-term treatment study analysis also showed similar results in topiroxostat subjects at all doses: 3.6% (13/361 subjects) for ALT and 1.1% (4/361 subjects) for AST.

The pooled double-blind study analysis and the pooled long-term treatment study analysis revealed treatment discontinuation in only 2 of 18 topiroxostat subjects who had ALT of ≥3 times the upper limit of normal, and the outcome after discontinuation was "disappeared" in both subjects. In addition, among the 16 subjects who continued treatment with topiroxostat, only 1 subject experienced serious "ALT increased" after the end of treatment, with an outcome of "disappeared." In association with topiroxostat treatment, no subject experienced increases in transaminases (≥3 times the upper limit of normal) accompanied by an increase in total bilirubin (≥1.5 times the upper limit of normal). The percentage of subjects who experienced increases in total bilirubin or alkaline phosphatase (ALP) up to ≥1.5 times the upper limit of normal due to topiroxostat treatment was similar between the placebo group and topiroxostat group (all doses pooled): 4.4% (6 of 135 subjects) and 3.9% (18 of 465 subjects), respectively, for total bilirubin and 0.7% (1 of 135 subjects) and 0.9% (4 of 465 subjects), respectively, for ALP.

Based on the above, although the incidence of the adverse events related to hepatic laboratory values was high in the topiroxostat group, the risk of the occurrence of serious adverse events should be low because serious adverse events were infrequent. However, given that adverse events and adverse drug reactions related to hepatobiliary disorders or abnormal hepatic laboratory values (e.g. "ALT increased" and "γ-GTP increased") tended to occur frequently by the sixth month of the maintenance phase in long-term treatment studies, the hepatic functions need to be monitored after the start of topiroxostat treatment to prevent serious hepatic disorder. A caution statement will be included in the proposed package insert.

PMDA considers as follows:
Given the cases of serious liver disorder and transaminase elevations observed during the long-term treatment studies, hepatic function monitoring should be advised in the package insert and it is necessary to continue to collect information on hepatopathy via post-marketing surveillance. The appropriateness of the caution statement in the package insert will be finalized, taking account of comments from the Expert Discussion.

4.(iii).B.(3).3) Kidney or bladder-related adverse events

The applicant explained as follows:
The incidence of major kidney or bladder-related adverse events from the pooled double-blind study

analysis[10] is shown in Table 59. No adverse events in the SOC "Renal and urinary disorders" occurred with an incidence of ≥1% in topiroxostat subjects at all doses. The incidence of major laboratory adverse events related to the kidney or bladder was higher in the topiroxostat group (all doses pooled) than in the placebo group except for "crystal urine present," but was lower than in the allopurinol group.

Table 59. Incidence of kidney or bladder-related adverse events in the pooled double-blind study analysis

	Placebo group (n = 135)	Topiroxostat group (all doses pooled) (n = 465)	Allopurinol group (n = 144)	Topiroxostat maintenance-phase dose group (n = 328)	Topiroxostat 120 mg/day group (n = 201)	Topiroxostat 160 mg/day group (n = 127)
SOC "Renal and urinary disorders"	0.7 (1)	1.1 (5)	0.0 (0)	0.6 (2)	0.0 (0)	1.6 (2)
Calculus ureteric	0.0 (0)	0.2 (1)	0.0 (0)	0.3 (1)	0.0 (0)	0.8 (1)
Calculus urinary	0.0 (0)	0.2 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Nephrolithiasis	0.7 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Pollakiuria	0.0 (0)	0.4 (2)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Renal cyst	0.0 (0)	0.2 (1)	0.0 (0)	0.3 (1)	0.0 (0)	0.8 (1)
β2 microglobulin urine increased	3.0 (4)	6.2 (29)	17.4 (25)	8.2 (27)	10.4 (21)	4.7 (6)
NAG increased	5.2 (7)	11.6 (54)	18.8 (27)	11.9 (39)	15.9 (32)	5.5 (7)
α1 microglobulin increased	0.7 (1)	9.7 (45)	25.0 (36)	13.4 (44)	19.4 (39)	3.9 (5)
Blood creatinine increased	0.0 (0)	0.9 (4)	4.2 (6)	1.2 (4)	1.0 (2)	1.6 (2)
Crystal urine present	0.7 (1)	0.6 (3)	2.8 (4)	0.6 (2)	1.0 (2)	0.0 (0)

% incidence (number of subjects with events), MedDRA/J (ver.14.1)

The incidence of major kidney- or bladder-related adverse events in each treatment phase from the pooled long-term treatment study analysis[19] is shown in Table 60. No adverse events in the SOC "Renal and urinary disorders" occurred with an incidence of ≥2% in topiroxostat subjects at all doses. The incidence of "crystal urine present" was <2%. The severity of adverse events in "Renal and urinary disorders" and laboratory adverse events related to the kidney or bladder was mild except for "calculus urinary" (2 subjects) and "calculus ureteric" (1 subject), which were both moderate.

The time course showed that the incidence of "β2 microglobulin urine increased" and "α1 microglobulin increased" tended to decrease after the third month of the maintenance phase. The incidence of "NAG increased" did not differ significantly regardless of treatment phase. One subject experienced "blood creatinine increased" that was ≥2-fold the level seen during the run-in period. The study was discontinued due to calculus urinary (moderate, serious) at Week 17 of treatment with 120 mg/day of topiroxostat, but the subject recovered after treatment discontinuation. This subject had renal and hepatic impairment, and the creatinine level exceeded the upper limit of normal even during the run-in period. The subject had concurrent "calculus urinary" before study initiation, and was considered to have experienced its spontaneous progression. A causal relationship with the study drug was ruled out. No crystals were detected in the urinary sediment.

Table 60. Incidence of initial major kidney- or bladder-related adverse events in each treatment phase in the pooled long-term treatment study analysis

	Total of topiroxostat group (all doses pooled) (n = 361)	Initial phase (6 weeks) (n = 361)	Before 3rd month of maintenance phase (n = 345)	3rd to 6th month of maintenance phase (n = 330)	6th to 9th month of maintenance phase (n = 166)	9th to 12th month of maintenance phase (n = 105)	After 12th month of maintenance phase (n = 105)
SOC "Renal and urinary disorders"	5.0 (18)	0.3 (1)	2.0 (7)	1.8 (6)	0.6 (1)	2.9 (3)	0.0 (0)
Calculus ureteric	1.1 (4)	0.0 (0)	0.3 (1)	0.6 (2)	0.0 (0)	1.0 (1)	0.0 (0)
Calculus urinary	0.6 (2)	0.0 (0)	0.6 (2)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Dysuria	0.3 (1)	0.0 (0)	0.3 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Nephrocalcinosis	0.3 (1)	0.0 (0)	0.3 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Nephrolithiasis	1.4 (5)	0.0 (0)	0.3 (1)	0.9 (3)	0.6 (1)	0.0 (0)	0.0 (0)
Pollakiuria	0.8 (3)	0.3 (1)	0.3 (1)	0.0 (0)	0.0 (0)	1.0 (1)	0.0 (0)
Renal cyst	0.6 (2)	0.0 (0)	0.0 (0)	0.3 (1)	0.0 (0)	1.0 (1)	0.0 (0)
Urinary retention	0.3 (1)	0.0 (0)	0.0 (0)	0.3 (1)	0.0 (0)	0.0 (0)	0.0 (0)
β2 microglobulin urine increased	20.5 (74)	6.1 (22)	8.4 (29)	3.9 (13)	4.2 (7)	1.9 (2)	1.0 (1)
NAG increased	24.1 (87)	8.6 (31)	7.5 (26)	4.5 (15)	3.0 (5)	6.7 (7)	2.9 (3)
α1 microglobulin increased	20.2 (73)	7.5 (27)	6.1 (21)	5.2 (17)	3.0 (5)	1.9 (2)	1.0 (1)
Blood creatinine increased	4.4 (16)	0.6 (2)	1.7 (6)	1.2 (4)	0.6 (1)	2.9 (3)	0.0 (0)
Crystal urine present	1.7 (6)	0.0 (0)	1.2 (4)	0.3 (1)	0.6 (1)	0.0 (0)	0.0 (0)

% incidence (number of subjects with events), MedDRA/J (ver.14.1)

The pooled double-blind study analysis identified calculi (calculus ureteric, calculus urinary, nephrolithiasis) during clinical studies in 2 subjects in the topiroxostat group regardless of dose (2 events) and 1 subject in the placebo group (1 event). In both cases in the topiroxostat group, the dose at which the calculus was observed was 80 mg/day. Calculi were observed in 10 subjects (11 events) in the long-term treatment studies, and occurred at a dose of 120 mg/day or 160 mg/day of topiroxostat in all subjects except for 1 subject (200 mg/day). Among the 13 events in 12 subjects in the topiroxostat group, a causal relationship with the study drug was ruled out except for 1 event in 1 subject in a double-blind study and 1 event in 1 subject in a long-term treatment study (1 event/subject each of "calculus ureteric" and "nephrolithiasis"). The severity of the 13 events in 12 subjects in the topiroxostat group was mild except for "calculus urinary" in 2 subjects (both in Study FYX-051-332) and "calculus ureteric" in 1 subject (Study FY1002), identified in the pooled long-term treatment study analysis. The severity of the 2 aforementioned events was moderate.

Based on the above, kidney or bladder-related adverse events are unlikely to become major clinical problems.

PMDA considers as follows:

Among kidney- or bladder-related adverse events, the incidence of "blood creatinine increased," albeit not higher than in the allopurinol (comparator) group, showed no tendency to decrease over the course of treatment in the long-term treatment studies. Furthermore, in the subject who experienced calculus urinary (serious) leading to study discontinuation, the blood creatinine level showed a ≥2-fold increase in comparison with the run-in period. In addition, given that renal impairment occurred in rodents due to xanthine crystal deposition in the kidney [see "3.(iii).B.(1) Nephrotoxicity"], and that the incidence of "β2 microglobulin urine increased," "NAG increased," and "α1 microglobulin increased" was high in the double-blind studies and the long-term treatment studies in patients, collection of information on kidney- or bladder-related adverse events needs to be continued in the post-marketing surveillance.

4.(iii).B.(3).4) Cutaneous adverse events

The applicant explained as follows:

Cutaneous adverse events were reviewed because a non-clinical study (rat distribution study [4.2.2.3-1]) showed a high rate of topiroxostat transfer to the skin. The pooled double-blind study analysis[10] revealed the following incidence of adverse events in the SOC "Skin and subcutaneous tissue disorders": 6.7% (9 of 135 subjects) in the placebo group, 4.5% (21 of 465 subjects) in the topiroxostat group (all doses pooled), 5.5% (18 of 328 subjects) in the topiroxostat maintenance-phase dose group, and 4.9% (7 of 144 subjects) in the allopurinol group, with no major differences between the topiroxostat group and the placebo or allopurinol group. The incidence of adverse drug reactions was 0.7% (1 of 135 subjects) in the placebo group, 1.1% (5 of 465 subjects) in the topiroxostat group (all doses pooled), 1.2% (4 of 328 subjects) in the topiroxostat maintenance-phase dose group, and 0.7% (1 of 144 subjects) in the allopurinol group. Cutaneous adverse events leading to study discontinuation occurred in 1 subject in the placebo group, 4 subjects in the topiroxostat group (all doses pooled), and 1 subject in the allopurinol group. Among them, those classified as adverse drug reactions occurred in 1 subject (eczema) in the placebo group and 4 subjects in the topiroxostat group (all doses pooled) (rash, 2 subjects; drug eruption and eczema, 1 subject each). The severity of "eczema" in 1 subject in the placebo group and "rash" in 2 subjects in the topiroxostat group (all doses pooled) was mild, while "drug eruption" and "eczema" in subjects in the topiroxostat group (all doses pooled) were moderate. None of the cutaneous adverse events classified as adverse drug reactions leading to study discontinuation were classified as serious adverse events. Among the 4 subjects in the topiroxostat group (all doses pooled), the outcome in 3 subjects was "recovered (resolved)" for all events (rash, 2 subjects; drug eruption, 1 subject) around 1 month after treatment discontinuation while for "eczema" in 1 subject (Study FY1003), the outcome was "recovered (resolved)" around 3 months after treatment discontinuation.

The pooled long-term treatment study analysis[19] revealed the following incidence of adverse events in the SOC "Skin and subcutaneous tissue disorders": 9.4% (34 of 361 subjects) in the topiroxostat group (all doses pooled) and 9.5% (33 of 348 subjects) in the topiroxostat maintenance-phase dose group. Moderate adverse events occurred in 3 subjects in the topiroxostat group (all doses pooled) (dermatitis allergic, erythema multiforme, urticaria). The dose at which the event occurred was 120 mg/day or 160 mg/day in all subjects, and "erythema multiforme" and "urticaria" were classified as adverse drug reactions. In the subject who experienced "erythema multiforme" (Study FYX-051-332), treatment was continued until the end of the treatment period because at onset, it was assessed that continuation of treatment would not cause any problem. However, erythema did not resolve and later the subject required inpatient treatment. The event was therefore classified as a serious adverse event, and subsided approximately 1 month after completion of treatment. The study was discontinued in the subject who experienced "urticaria" (Study FYX-051-332), but this event "subsided" approximately 3 months after discontinuation, and was nonserious. The incidence of adverse drug reactions was 2.2% (8 of 361 subjects) in the topiroxostat group (all doses pooled) and 2.3% (8 of 348 subjects) in the topiroxostat maintenance-phase dose group. Cutaneous adverse events leading to study

discontinuation occurred in 6 subjects in the topiroxostat group (all doses pooled) (drug eruption, erythema, urticaria, rash, cold sweat, eczema, 1 subject each). The dose was 120 mg/day at the onset of "drug eruption," "erythema," "urticaria," and "eczema," and was 80 mg/day at the onset of "rash" and "cold sweat." Severity was moderate for "urticaria" and mild for other events, while all were nonserious events. Five out of 6 events were classified as adverse drug reactions with the exception of 1 event (eczema at 120 mg/day). Among the 5 events classified as adverse drug reactions, the outcome of 4 events was "recovered (resolved)" around 1 month after discontinuation, and the remaining 1 event was "urticaria" described above.

Although the association between cutaneous adverse events and drug-induced hypersensitivity syndrome may cause concern, given that the subjects in whom cutaneous adverse events occurred did not experience any adverse events that are believed to occur frequently in drug-induced hypersensitivity syndrome, i.e. pyrexia, leukocytosis, occurrence of atypical lymphocytes, and eosinophilia, the association with drug-induced hypersensitivity syndrome is unlikely. Based on the absence of severe events, cutaneous adverse events are not considered to become a problem in the use of topiroxostat.

While PMDA accepted the above explanation, it considers that collection of information on cutaneous adverse events needs to be continued via post-marketing surveillance because cutaneous adverse events included serious "erythema multiforme," and cutaneous adverse drug reactions have been reported and a caution statement has been provided for drugs in the same class. The relevance of a caution statement in the package insert will be finalized, taking into account the comments made in the Expert Discussion.

4.(iii).B.(4) Indications

PMDA considers as follows:

The Japanese clinical studies on topiroxostat were conducted in patients with hyperuricaemia including gout, and similar efficacy has been demonstrated irrespective of different clinical diagnoses (gout vs. hyperuricaemia) [see "4.(iii).B.(2) Efficacy"]. In addition, the Japanese guideline recommends treatment of hyperuricaemia aimed at prevention of the onset of gout arthritis as an indication for antihyperuricaemic treatment. Based on the above, there should be no problem in selecting "gout and hyperuricaemia" as the indications for topiroxostat.

4.(iii).B.(5) Dosage and administration

The applicant explained as follows:

The phase I multiple dose study (Study FYX-051-112) compared the decrease in plasma uric acid level from baseline (ΔEC), which was greater in the topiroxostat 80 mg (in 2 doses) group, i.e. treated with twice-daily 40-mg doses, than in the 80 mg (in 1 dose) group, i.e. treated with once-daily 80-mg dose (Table 14). The serum uric acid-lowering effect of twice daily administration was greater in the topiroxostat 160 mg (in 2 doses) group than in the topiroxostat 80 mg (in 2 doses) group. In the late

phase II study (Study FYX-051-323), the percentage decrease in serum uric acid level (mean ± SD) from baseline at the end of treatment was similar between 120 and 160 mg/day of topiroxostat: 40.92% ± 9.84% (n = 39) and 44.79% ± 13.26% (n = 39), respectively. The phase III study (Study FY1001) compared the maintenance doses of topiroxostat at 120 mg/day and allopurinol at 200 mg/day, and demonstrated the non-inferiority of topiroxostat compared with allopurinol. The percentage of subjects who achieved the target serum uric acid level of ≤6.0 mg/dL at the end of treatment was similar between the topiroxostat group and the allopurinol group: 72.4% (71 of 98 subjects) and 73.3% (77 of 105 subjects), respectively. Based on the evidence cited above, 120 mg/day is considered to be an appropriate maintenance dose of topiroxostat.

The phase III long-term treatment studies (Studies FYX-051-332 and FY1002) investigated the effect of dose escalation when the effect of topiroxostat was insufficient at 120 mg/day. In Study FYX-051-332, 58 subjects had their dose increased to and maintained at 160 mg/day because the effect of topiroxostat was insufficient at 120 mg/day. In these subjects, the serum uric acid level and its percentage decrease were 6.94 ± 1.09 mg/dL and 30.57% ± 11.05% (n = 57), respectively, before the dose increase (at Week 18) and 6.13 ± 1.21 mg/dL and 38.74% ± 11.93% (n = 58), respectively, at the completion of treatment (LOCF), indicative of a further decrease in serum uric acid level at the completion of treatment from the level prior to the dose increase. The percentage decrease [two-sided 95% CI] in serum uric acid level, specific to the final topiroxostat dose, was 39.73% [37.90, 41.56] at 120 mg/day (n = 173) and 38.74% [35.60, 41.87] at 160 mg/day (n = 58).

In Study FY1002, the dose was increased to 160 mg/day when the effect of topiroxostat was insufficient at 120 mg/day, and the dose was increased further to 200 mg/day and then to 240 mg/day when the effect was still insufficient. The dose was not increased in subjects whose dose was maintained at 120 or 160 mg/day at the time points to assess the applicability of dose increase, even if the serum uric acid level exceeded 6.0 mg/dL at subsequent dose-increase timing. The results showed that 18 subjects had their dose increased to and maintained at 160 mg/day, and the serum uric acid level and its percentage decrease in these subjects were 6.43 ± 1.03 mg/dL (LOCF) and 31.46% ± 13.39% (LOCF), respectively, before the dose increase (at Week 18) and 5.40 ± 0.98 mg/dL (LOCF) and 42.60% ± 12.51% (LOCF), respectively, at the completion of treatment, indicative of a downward trend in serum uric acid level at the completion of treatment from the level prior to the dose increase. The percentage decrease [two-sided 95% CI] in serum uric acid level, specific to the final topiroxostat dose, was 38.60% [35.76, 41.44] at 120 mg/day (n = 84), 42.60% [36.38, 48.83] at 160 mg/day (n = 18), and 40.88% [35.50, 46.25] at ≥200 mg/day (n = 13), suggesting a plateau in the serum uric acid-lowering effect at ≥200 mg/day as compared with 120 and 160 mg/day. Meanwhile, in the long-term treatment studies, the incidence of adverse events and adverse drug reactions, specific to the final topiroxostat dose, was higher at ≥200 mg/day: 100.0% (13 of 13 subjects) and 53.8% (7 of 13 subjects), respectively, than at ≤160 mg/day (n = 348): 88.5% (308 of 348 subjects) and 39.9% (139 of 348 subjects), respectively, albeit the number of assessable subjects treated at ≥200 mg/day was small (n = 13).

A decrease in serum uric acid level is expected to reduce the occurrence of gout arthritis on a long-term basis. From a point of view to minimize the incidence of gout arthritis after the start of topiroxostat treatment, the initial administration procedure was investigated. The incidence of gout arthritis at 120 and 160 mg/day of topiroxostat was 12.0% to 16.2% and 20.0%, respectively, in 1-step dose escalation studies (Studies FYX-051-221 and FYX-051-222), but tended to be lower in 2-step dose escalation studies (Studies FYX-051-323, FY1001, and FY1003): 5.1% to 12.0% and 5.0% to 14.5%, respectively (Table 55). Therefore, gradual dose escalation as recommended in the Japanese guideline is considered to reduce the occurrence of gout arthritis during topiroxostat treatment.

Based on the above, 60 mg twice daily was selected as the maintenance dose, with an increase to 80 mg twice daily if the effect is insufficient. A 2-step dose escalation procedure will be recommended in the "Precautions for dosage and administration" section of the proposed package insert to reduce the occurrence of gout arthritis during the early phase of topiroxostat treatment.

PMDA considers as follows:
There is no problem in selecting 60 mg twice daily as the usual maintenance dose, with possible dose increase to 80 mg twice daily in cases where the effect is insufficient. In addition, it is appropriate to recommend a 2-step dose escalation procedure in the "Precautions for dosage and administration" section in order to reduce the occurrence of gout arthritis during the early phase of topiroxostat treatment.

4.(iii).B.(6) Special populations

4.(iii).B.(6).1) Patients with renal impairment

The applicant explained as follows:
Pharmacokinetic analysis of topiroxostat showed that the urinary fractional excretion of unchanged topiroxostat is <0.1%, and that topiroxostat is excreted as N_1- and N_2-glucuronide conjugates, and topiroxostat N-oxide. Therefore, the effect of decreased renal function on the plasma concentration of unchanged topiroxostat is considered to be minor [see "4.(ii).B.(1) Pharmacokinetics and pharmacodynamics in patients with severe renal impairment"]. The efficacy results from the pooled double-blind study analysis[10] showed the percentage decrease in serum uric acid level, specific to the baseline eGFR[59] (mL/min/1.73m^2), in Table 61. There were no major differences in the serum uric acid-lowering effect of topiroxostat regardless of the level of renal function.

[59] eGFR was calculated from serum creatinine level (Scr) using the formula: $eGFR = 194 \times Scr^{-1.094} \times age^{-0.287}$ for males; $eGFR = 0.739 \times 194 \times Scr^{-1.094} \times age^{-0.287}$ for females.

Table 61. Percentage decrease in serum uric acid level in each baseline eGFR range in the pooled double-blind study analysis (FAS, LOCF)

	Placebo group			Topiroxostat 120 mg/day group[a)]			Topiroxostat 160 mg/day group[a)]		
Baseline eGFR ($mL/min/1.73m^2$)	< 60 (n = 67)	≥ 60 < 90 (n =51)	≥ 90 (n = 17)	< 60 (n = 29)	≥ 60 < 90 (n = 143)	≥ 90 (n = 27)	< 60 (n = 63)	≥ 60 < 90 (n = 53)	≥ 90 (n = 8)
Percentage decrease in serum uric acid level (%)	-0.40 ± 9.95	0.82 ± 11.28	4.97 ± 12.50	39.05 ± 13.08	35.42 ± 12.74	34.73 ± 13.09	45.04 ± 21.12	45.12 ± 13.11	47.86 ± 8.61

Mean ± SD
a) Final dose level

In Study FY1003, topiroxostat was administered to subjects with concurrent moderate renal impairment, initially at 120 mg/day without dose adjustment, and then at an increased dose of 160 mg/day in all subjects unless the study was discontinued. The serum uric acid level and its percentage decrease (mean ± SD) was 4.87 ± 1.35 mg/dL and 41.31% ± 17.47% (n = 59), respectively, before the dose increase (at Week 14) and 4.51 ± 1.52 mg/dL and 45.38% ± 21.80% (n = 60), respectively, at the end of treatment (LOCF). Subjects whose uric acid level was >6.0 mg/dL at Week 14 (n = 12) had the following serum uric acid level and percentage decrease: 6.87 ± 0.97 mg/dL and 18.94% ± 21.94%, respectively, before the dose increase (at Week 14) and 6.22 ± 1.90 mg/dL and 24.67% ± 36.49%, respectively, at the end of treatment (LOCF). Therefore, a dose increase to 160 mg/day is expected to be effective also in patients with concurrent moderate renal impairment if the effect at a dose of 120 mg/day is insufficient.

The safety results from the pooled double-blind study analysis[10] showed the incidence of kidney- or bladder-related adverse events, specific to the baseline eGFR, in Table 62. There were no major differences in the incidence regardless of the level of renal function in the topiroxostat, placebo, or allopurinol group. In the topiroxostat group (all doses pooled), "gout arthritis" was a major adverse event with an incidence higher in the subjects with eGFR of <60 than in those with eGFR of ≥90.

Table 62. Incidence of kidney- or bladder-related adverse events in each baseline eGFR range in the pooled double-blind study analysis

	Placebo group			Topiroxostat group (all doses pooled)			Topiroxostat maintenance-phase dose group			Allopurinol group		
Baseline eGFR ($mL/min/1.73m^2$)	< 60	≥ 60 < 90	≥ 90	< 60	≥ 60 < 90	≥ 90	< 60	≥ 60 < 90	≥ 90	< 60	≥ 60 < 90	≥ 90
Number of subjects	n = 67	n = 51	n = 17	n = 106	n = 302	n = 57	n = 94	n = 198	n = 36	n = 22	n = 106	n = 16
Any adverse event	71.6 (48)	68.6 (35)	82.4 (14)	72.6 (77)	73.8 (223)	77.2 (44)	73.4 (69)	76.8 (152)	75.0 (27)	77.3 (17)	84.0 (89)	93.8 (15)
Gout arthritis	6.0 (4)	7.8 (4)	11.8 (2)	13.2 (14)	10.9 (33)	5.3 (3)	13.8 (13)	12.6 (25)	2.8 (1)	0.0 (0)	6.6 (7)	31.3 (5)
SOC "Renal and urinary disorders"	0.0 (0)	2.0 (1)	0.0 (0)	2.8 (3)	0.3 (1)	1.8 (1)	2.1 (2)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
β2 microglobulin urine increased	3.0 (2)	0.0 (0)	11.8 (2)	6.6 (7)	6.6 (20)	3.5 (2)	7.4 (7)	9.1 (18)	5.6 (2)	22.7 (5)	16.0 (17)	18.8 (3)
NAG increased	0.0 (0)	7.8 (4)	17.6 (3)	5.7 (6)	13.6 (41)	12.3 (7)	5.3 (5)	14.6 (29)	13.9 (5)	18.2 (4)	18.9 (20)	18.8 (3)
α1 microglobulin increased	1.5 (1)	0.0 (0)	0.0 (0)	6.6 (7)	10.9 (33)	8.8 (5)	7.4 (7)	16.2 (32)	13.9 (5)	27.3 (6)	23.6 (25)	31.3 (5)
Blood creatinine increased	0.0 (0)	0.0 (0)	0.0 (0)	1.9 (2)	0.7 (2)	0.0 (0)	2.1 (2)	1.0 (2)	0.0 (0)	4.5 (1)	4.7 (5)	0.0 (0)

% incidence (number of subjects with events), MedDRA/J (ver.14.1)

The incidence of adverse events, specific to the baseline eGFR, from the pooled long-term treatment study analysis,[19] is shown in Table 63. There were no major differences regardless of the level of renal function.

Table 63. Incidence of kidney or bladder-related adverse events in each baseline eGFR range in the pooled long-term treatment study analysis

	Topiroxostat group (all doses pooled)			Topiroxostat maintenance-phase dose group		
Baseline eGFR ($mL/min/1.73m^2$)	< 60 (n = 70)	≥ 60 < 90 (n = 234)	≥ 90 (n = 57)	< 60 (n = 66)	≥ 60 < 90 (n = 227)	≥ 90 (n = 55)
Any adverse event	91.4 (64)	88.0 (206)	89.5 (51)	90.9 (60)	87.7 (199)	89.1 (49)
Gout arthritis	12.9 (9)	10.7 (25)	10.5 (6)	12.1 (8)	11.0 (25)	9.1 (5)
SOC "Renal and urinary disorders"	7.1 (5)	5.6 (13)	0.0 (0)	7.6 (5)	5.3 (12)	0.0 (0)
β2 microglobulin urine increased	28.6 (20)	19.2 (45)	15.8 (9)	27.3 (18)	18.5 (42)	14.5 (8)
NAG increased	27.1 (19)	19.2 (45)	40.4 (23)	28.8 (19)	19.8 (45)	38.2 (21)
α1 microglobulin increased	22.9 (16)	19.7 (46)	19.3 (11)	22.7 (15)	19.8 (45)	16.4 (9)
Blood creatinine increased	5.7 (4)	5.1 (12)	0.0 (0)	4.5 (3)	5.3 (12)	0.0 (0)

% incidence (number of subjects with events), MedDRA/J (ver.14.1)

The applicant considers that the above findings show the absence of safety or efficacy problems specific to patients with concurrent mild and moderate renal impairment. Nevertheless, careful administration in patients with severe renal impairment will be advised because of the lack of clinical experience in these patients.

PMDA considers as follows:

PMDA accepts the applicant's explanation that, based on the clinical study results, dose adjustment is not required for the administration of topiroxostat to patients with concurrent mild and moderate renal impairment. However, given that patients with renal impairment are susceptible to hyperuricaemia, that the Japanese guideline recommends selection of XOR inhibitors instead of uricosuric agents for patients with moderate or more severe renal impairment, and that the safety and efficacy have not been studied in patients with severe renal impairment, it is necessary to advise careful administration in patients with severe renal impairment in the package insert, and to continue collecting information on safety in patients with renal impairment via the post-marketing surveillance.

4.(iii).B.(6).2) Patients with hepatic impairment

The applicant explained as follows:

The efficacy results from the pooled double-blind study analysis[10] showed no major differences in the percentage decrease in serum uric acid level by topiroxostat between subjects with and without concurrent hepatic disease at baseline (Table 64).

Table 64. Percentage decrease in serum uric acid level in subjects with and without concurrent hepatic disease at baseline in the pooled double-blind study analysis (FAS, LOCF)

	Placebo group		Topiroxostat 120 mg/day group[a)]		Topiroxostat 160 mg/day group[a)]	
Presence or absence of concurrent hepatic disease at baseline	Without complication (n = 102)	With complication (n = 33)	Without complication (n = 128)	With complication (n = 71)	Without complication (n = 96)	With complication (n = 28)
Percentage decrease in serum uric acid level (%)	0.26 ± 11.13	2.21 ± 9.98	36.07 ± 13.48	35.46 ± 11.69	46.37 ± 13.82	41.44 ± 26.17

Mean ± SD

a) Final dose level

The safety results from the pooled double-blind study analysis and the pooled long-term treatment study analysis[19] showed no major differences in the incidence of hepatic adverse events between

subjects with and without concurrent hepatic disease (Tables 65 and 66). The SOC in which the incidence in the topiroxostat group (all doses pooled) differed by ≥10% due to the presence of concurrent hepatic disease was "Investigations." Among major hepatic adverse events in the SOC "Investigations" identified in the pooled double-blind study analysis, the incidence of "ALT increased" and "AST increased" in the topiroxostat group (all doses pooled) was higher in subjects "with complications" than in those "without complications"; the incidence of "ALT increased" and "AST increased" in the allopurinol group was also higher in subjects "with complications" than in those "without complications." Among major hepatic adverse events in the SOC "Investigations" identified in the pooled long-term treatment study analysis, the incidence of "ALT increased" did not differ between subjects "with complications" and those "without complications," while the incidence of "AST increased" was higher in subjects "with complications" than in those "without complications." The incidence of "blood bilirubin increased" was also higher in subjects "with complications" than in those "without complications."

The above findings show that, although the incidence of "ALT increased" and "AST increased" in the topiroxostat group was higher in subjects "with complications," i.e. with hepatic disease, than those "without complications," a similar trend was also observed in the allopurinol group. Therefore, there are no particular concerns in treatment with topiroxostat. Nevertheless, careful administration will be advised in patients with hepatic impairment because clinical experience in such patients is limited due to exclusion of patients with ALT or AST of ≥100 IU/L from clinical studies.

Table 65. Incidence of hepatic adverse events in subjects with and without concurrent hepatic disease in the pooled double-blind study analysis

	Placebo group		Topiroxostat group (all doses pooled)		Topiroxostat maintenance-phase dose group		Allopurinol group	
Presence or absence of concurrent hepatic disease at baseline	Without complication (n = 102)	With complication (n = 33)	Without complication (n = 348)	With complication (n = 117)	Without complication (n = 228)	With complication (n = 100)	Without complication (n = 94)	With complication (n = 50)
Any adverse event	75.5 (77)	60.6 (20)	71.3 (248)	82.1 (96)	71.9 (164)	84.0 (84)	80.9 (76)	90.0 (45)
SOC "Hepatobiliary disorders"	0.0 (0)	3.0 (1)	0.0 (0)	2.6 (3)	0.0 (0)	3.0 (3)	0.0 (0)	0.0 (0)
ALT increased	2.9 (3)	9.1 (3)	10.9 (38)	17.1 (20)	11.0 (25)	20.0 (20)	6.4 (6)	12.0 (6)
AST increased	3.9 (4)	3.0 (1)	9.8 (34)	17.1 (20)	11.4 (26)	18.0 (18)	4.3 (4)	22.0 (11)
Blood bilirubin increased	1.0 (1)	0.0 (0)	2.0 (7)	1.7 (2)	1.3 (3)	2.0 (2)	3.2 (3)	2.0 (1)
γ-GTP increased	2.9 (3)	9.1 (3)	7.2 (25)	8.5 (10)	7.0 (16)	9.0 (9)	3.2 (3)	8.0 (4)
Blood alkaline phosphatase increased	0.0 (0)	3.0 (1)	1.1 (4)	3.4 (4)	0.9 (2)	4.0 (4)	0.0 (0)	2.0 (1)

% incidence (number of subjects with events), MedDRA/J (ver.14.1)

Table 66. Incidence of hepatic adverse events in subjects with and without concurrent hepatic disease in the pooled long-term treatment study analysis

	Topiroxostat group (all doses pooled)		Topiroxostat maintenance-phase dose group	
Presence or absence of concurrent hepatic disease at baseline	Without complication (n = 228)	With complication (n = 133)	Without complication (n = 219)	With complication (n = 129)
Any adverse event	89.0 (203)	88.7 (118)	88.6 (194)	88.4 (114)
SOC "Hepatobiliary disorders"	3.9 (9)	5.3 (7)	3.7 (8)	5.4 (7)
ALT increased	23.7 (54)	21.1 (28)	24.2 (53)	20.9 (27)
AST increased	14.0 (32)	25.6 (34)	13.7 (30)	25.6 (33)
Blood bilirubin increased	1.3 (3)	5.3 (7)	1.4 (3)	5.4 (7)
γ-GTP increased	11.8 (27)	10.5 (14)	11.4 (25)	9.3 (12)
Blood alkaline phosphatase increased	0.9 (2)	1.5 (2)	0.9 (2)	1.6 (2)

% incidence (number of subjects with events), MedDRA/J (ver.14.1)

PMDA accepts the applicant's explanation, but taking into account that a high γ-GTP level had been observed as early as during the run-in period in the subject who experienced serious hepatic impairment in Study FYX-051-332, it is necessary to provide appropriate advice on administration in patients with hepatic impairment, and to continue collecting information on safety in patients with hepatic impairment in the post-marketing surveillance.

4.(iii).B.(6).3) Elderly patients

The applicant explained as follows:

The pharmacokinetic studies in elderly male patients and non-elderly male patients showed no differences sufficient to cause concern [see "4.(ii).A.(3).2) Pharmacokinetic and pharmacodynamic study in elderly men"]. The efficacy results from the pooled double-blind study analysis[10] showed the percentage decrease in serum uric acid level specific to the baseline age in Table 67, with no major age-related differences in the serum uric acid-lowering effect of topiroxostat.

Table 67. Percentage decrease in serum uric acid level specific to baseline age in the pooled double-blind study analysis (FAS, LOCF)

	Placebo group		Topiroxostat 120 mg/day group		Topiroxostat 160 mg/ day group	
Age (year)	< 65 (n = 99)	≥ 65 (n = 36)	< 6 (n = 183)	≥ 65 (n = 16)	< 65 (n = 91)	≥ 65 (n = 33)
Percentage decrease in serum uric acid level (%)	1.17 ± 11.22	-0.45 ± 9.83	35.33 ± 12.85	41.84 ± 11.57	43.34 ± 18.56	50.54 ± 12.38

Mean ± SD

The use of topiroxostat during clinical studies involved 135 elderly patients, 132 of whom were treated at maintenance-phase doses (120 mg/day or 160 mg/day). The pooled double-blind study analysis[10] identified the following adverse events that occurred in ≥10% of subjects in any of the placebo group, topiroxostat group (all doses pooled), topiroxostat maintenance-phase dose group, or allopurinol group: "nasopharyngitis," "ALT increased," "AST increased," "β2 microglobulin increased," "NAG increased," "blood creatine phosphokinase increased," "blood triglycerides increased," "α1 microglobulin increased," and "gout arthritis." The age-specific incidence of these adverse events (<65 years, ≥65 and <70 years, ≥70 years) is shown in Table 68. The incidences of adverse events and adverse drug reactions in the topiroxostat group (all doses pooled) were 73.5% (305 of 415 subjects) and 30.6% (127 of 415 subjects), respectively, at age of <65, 72.0% (18 of 25 subjects) and 28.0% (7 of 25 subjects), respectively, at age of ≥65 and <70, and 84.0% (21 of 25 subjects) and 48.0% (12 of 25 subjects), respectively, at age of ≥70. The incidence of major adverse events did not tend to increase with age, and the adverse events that tended to increase with age showed a similar trend in the allopurinol group.

Table 68. Age-specific incidence of major adverse events in the pooled double-blind study analysis

	Placebo group			Topiroxostat group (all doses pooled)			Topiroxostat maintenancee-phase dose group			Allopurinol group		
Age (years)	< 65	≥ 65 < 70	≥ 70	< 65	≥ 65 < 70	≥ 70	< 65	≥ 65 < 70	≥ 70	< 65	≥ 65 < 70	≥ 70
Number of subjects	n = 99	n = 13	n = 23	n = 415	n = 25	n = 25	n = 278	n = 25	n = 25	n = 123	n = 9	n = 12
Any adverse event	72.7 (72)	76.9 (10)	65.2 (15)	73.5 (305)	72.0 (18)	84.0 (21)	75.2 (209)	72.0 (18)	84.0 (21)	82.1 (101)	88.9 (8)	100.0 (12)
Nasopharyngitis	21.2 (21)	15.4 (2)	26.1 (6)	14.5 (60)	12.0 (3)	12.0 (3)	16.9 (47)	12.0 (3)	12.0 (3)	9.8 (12)	0.0 (0)	25.0 (3)
ALT increased	6.1 (6)	0.0 (0)	0.0 (0)	12.5 (52)	20.0 (5)	4.0 (1)	14.0 (39)	20.0 (5)	4.0 (1)	8.1 (10)	22.2 (2)	0.0 (0)
AST increased	4.0 (4)	7.7 (1)	0.0 (0)	11.6 (48)	16.0 (4)	8.0 (2)	13.7 (38)	16.0 (4)	8.0 (2)	9.8 (12)	11.1 (1)	16.7 (2)
β2 microglobulin increased	1.0 (1)	0.0 (0)	0.0 (0)	3.1 (13)	12.0 (3)	16.0 (4)	4.0 (11)	12.0 (3)	16.0 (4)	8.1 (10)	11.1 (1)	50.0 (6)
NAG increased	7.1 (7)	0.0 (0)	0.0 (0)	11.8 (49)	4.0 (1)	16.0 (4)	12.2 (34)	4.0 (1)	16.0 (4)	20.3 (25)	0.0 (0)	16.7 (2)
Blood creatine phosphokinase increased	6.1 (6)	0.0 (0)	4.3 (1)	10.1 (42)	20.0 (5)	12.0 (3)	10.1 (28)	20.0 (5)	12.0 (3)	13.0 (16)	0.0 (0)	33.3 (4)
Blood triglycerides increased	4.0 (4)	7.7 (1)	4.3 (1)	11.3 (47)	12.0 (3)	20.0 (5)	14.4 (40)	12.0 (3)	20.0 (5)	26.0 (32)	33.3 (3)	41.7 (5)
α1 microglobulin increased	0.0 (0)	7.7 (1)	0.0 (0)	9.4 (39)	8.0 (2)	16.0 (4)	13.7 (38)	8.0 (2)	16.0 (4)	24.4 (30)	33.3 (3)	25.0 (3)
Gout arthritis	7.1 (7)	23.1 (3)	0.0 (0)	11.1 (46)	4.0 (1)	12.0 (3)	12.6 (35)	4.0 (1)	12.0 (3)	9.8 (12)	0.0 (0)	0.0 (0)

% incidence (number of subjects with events), MedDRA/J (ver.14.1)

The pooled long-term treatment study analysis[19] identified the following adverse events that occurred in ≥10% of subjects in either of the topiroxostat group (all doses pooled) or in the topiroxostat maintenance-phase dose group: "nasopharyngitis," "ALT increased," "AST increased," "β2 microglobulin urine increased," "NAG increased," "blood creatine phosphokinase increased," "blood triglycerides increased," "γ-GTP increased," "α1 microglobulin increased," and "gout arthritis." The age-specific incidence (<65 years, ≥65 years and <70 years, ≥70 years) of these adverse events (Table 69) showed no tendency towards an increase in the incidence of major adverse events with age.

Table 69. Age-specific incidence of major adverse events in the pooled long-term treatment study analysis

	Topiroxostat group (all doses pooled)			Topiroxostat maintenance-phase dose group		
Age (year)	< 65 (n = 276)	≥ 65 and < 70 (n = 55)	≥ 70 (n = 30)	< 65 (n = 266)	≥ 65 and < 70 (n = 52)	≥ 70 (n = 30)
Any adverse event	88.4 (244)	94.5 (52)	83.3 (25)	88.0 (234)	94.2 (49)	83.3 (25)
Nasopharyngitis	25.0 (69)	20.0 (11)	23.3 (7)	25.2 (67)	19.2 (10)	23.3 (7)
ALT increased	25.4 (70)	16.4 (9)	10.0 (3)	25.6 (68)	17.3 (9)	10.0 (3)
AST increased	20.7 (57)	16.4 (9)	0.0 (0)	20.3 (54)	17.3 (9)	0.0 (0)
β2 microglobulin urine increased	17.8 (49)	32.7 (18)	23.3 (7)	16.5 (44)	32.7 (17)	23.3 (7)
NAG increased	23.2 (64)	30.9 (17)	20.0 (6)	23.3 (62)	32.7 (17)	20.0 (6)
Blood creatine phosphokinase increased	15.6 (43)	10.9 (6)	13.3 (4)	15.8 (42)	11.5 (6)	13.3 (4)
Blood triglycerides increased	21.7 (60)	12.7 (7)	13.3 (4)	21.1 (56)	13.5 (7)	13.3 (4)
γ-GTP increased	12.7 (35)	7.3 (4)	6.7 (2)	12.0 (32)	5.8 (3)	6.7 (2)
α1 microglobulin increased	19.2 (53)	23.6 (13)	23.3 (7)	18.8 (50)	23.1 (12)	23.3 (7)
Gout arthritis	11.2 (31)	14.5 (8)	3.3 (1)	11.3 (30)	13.5 (7)	3.3 (1)

% incidence (number of subjects with events), MedDRA/J (ver.14.1)

PMDA accepts the applicant's explanation that no safety problems have been identified in the use of topiroxostat in elderly patients. However, given the limited numbers of elderly subjects evaluated in clinical studies, PMDA considers it necessary to continue collecting information on safety in elderly patients in the post-marketing surveillance.

4.(iii).B.(6).4) Female patients

The applicant explained as follows:

The pharmacokinetic studies in elderly female patients and elderly male patients detected no

gender-related differences [see "4.(ii).A.(3) Intrinsic factors"]. The efficacy results from the pooled double-blind study analysis[10] showed that, although gender-related effects were difficult to assess since only 2 female subjects were included in the topiroxostat 120 mg/day group, the percentage decrease in serum uric acid level (mean ± SD) in the topiroxostat 160 mg/day group was similar between men and women: 45.04% ± 17.89% (n = 113) and 47.49% ± 11.20% (n = 11), respectively. Also in the pooled long-term treatment study analysis,[19] the percentage decrease in serum uric acid level in the topiroxostat group (all doses pooled) was similar between men and women: 38.95% ± 12.53% (n = 352) and 39.35% ± 13.54% (n = 7), respectively. Therefore, the efficacy of topiroxostat is not considered to be affected by gender-related differences.

The safety results from the pooled double-blind study analysis revealed the following gender-specific incidence of adverse events: 71.8% (94 of 131 subjects) in men and 75.0% (3 of 4 subjects) in women in the placebo group; 73.2% (331 of 452 subjects) and 100.0% (13 of 13 subjects), respectively, in the topiroxostat group (all doses pooled); 74.6% (235 of 315 subjects) and 100.0% (13 of 13 subjects), respectively, in the topiroxostat maintenance-phase dose group; and 83.9% (120 of 143 subjects) and 100.0% (1 of 1 subject), respectively, in the allopurinol group. The incidence of adverse drug reactions in men and women was: 30.5% (40 of 131 subjects) and 0.0% (0 of 4 subjects), respectively, in the placebo group; 31.0% (140 of 452 subjects) and 46.2% (6 of 13 subjects), respectively, in the topiroxostat group (all doses pooled); 31.1% (98 of 315 subjects) and 46.2% (6 of 13 subjects), respectively, in the topiroxostat maintenance-phase dose group; and 27.3% (39 of 143 subjects) and 0.0% (0 of 1 subject), respectively, in the allopurinol group. In the long-term treatment studies, the incidence of adverse events in men and women was: 88.7% (314 of 354 subjects) and 100.0% (7 of 7 subjects), respectively, in the topiroxostat group (all doses pooled) and 88.3% (302 of 342 subjects) and 100.0% (6 of 6 subjects), respectively, in the topiroxostat maintenance-phase dose group, and the incidence of adverse drug reactions was: 40.7% (144 of 354 subjects) and 28.6% (2 of 7 subjects), respectively, in the topiroxostat group (all doses pooled) and 40.1% (137 of 342 subjects) and 33.3% (2 of 6 subjects), respectively, in the topiroxostat maintenance-phase dose group. No clear conclusion could be drawn because of the limited numbers of female subjects included in the clinical studies as shown above.

PMDA accepts the applicant's explanation. However, given the limited numbers of female subjects evaluated in clinical studies, PMDA considers it necessary to continue collecting information on safety in female patients in the post-marketing surveillance.

4.(iii).B.(7) Post-marketing surveillance

The applicant explained as follows:

A drug use-results survey (planned number of patients, 3000; observation period, 54 weeks) will be conducted in patients with gout or hyperuricaemia to study the safety and efficacy of topiroxostat in long-term clinical use.

PMDA considers it necessary to collect safety information on gout arthritis, hepatic impairment, kidney- and bladder-related adverse events, cutaneous adverse events, etc. as well as in patients with renal or hepatic impairment and elderly or female patients. The details of the proposed post-marketing surveillance plan will be finalized, taking the comments made at the Expert Discussion into account.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

To be reported later.

2. PMDA's conclusion on the results of GCP on-site inspection

To be reported later.

IV. Overall Evaluation

Based on the submitted data, it is concluded that the efficacy of the drug product in patients with gout or hyperuricaemia has been demonstrated and its safety is acceptable in view of its observed benefits. The drug product has clinical significance because it inhibits uric acid production and offers a new treatment option for gout and hyperuricaemia. PMDA considers it necessary to investigate as part of post-marketing surveillance safety information on gout arthritis, hepatic impairment, kidney and bladder-related adverse events, cutaneous adverse events etc. as well as in patients with renal or hepatic impairment and elderly or female patients.

PMDA considers that the drug product may be approved if it can be concluded based on comments from the Expert Discussion that there are no particular problems.

Review Report (2)

April 15, 2013

I. Product Submitted for Registration

[Brand name]	(a) Topiloric Tablets 20 mg, 40 mg, and 60 mg
	(b) Uriadec Tablets 20 mg, 40 mg, and 60 mg
[Non-proprietary name]	Topiroxostat
[Applicant]	(a) Fujiyakuhin Co., Ltd.
	(b) Sanwa Kagaku Kenkyusho Co., Ltd.
[Date of application]	June 26, 2012

II. Content of the Review

The outline of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is described in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA administrative Rule No. 8/2008 dated December 25, 2008).

(1) Efficacy

Taking into account the results for primary endpoints in the phase III study (Study FY1001) [Review Report (1), Table 37], the course of serum uric acid levels in the pooled long-term treatment study analysis [Review Report (1), Figure 3], and the study on efficacy for a specific clinical diagnosis (gout vs. hyperuricaemia) [Review Report (1), Table 51], PMDA considers that the efficacy of topiroxostat has been demonstrated. Given that febuxostat had not been approved when the phase III study (Study FY1001) was started (in 20[redacted]), it was appropriate that allopurinol, a drug in the same class (uric acid production inhibitors [XOR inhibitors]) as topiroxostat, was selected as the comparator for this study. The above conclusion by PMDA was supported by the expert advisors.

(2) Safety

(2).1) Hepatic impairment

Given the cases of serious liver disorder and "transaminases increased" observed during the long-term treatment studies, PMDA considered that hepatic function monitoring should be advised in the package insert, and collection of information on hepatic dysfunction needs to be continued via the post-marketing surveillance. The above conclusion by PMDA was supported by the expert advisors. Based on the above, PMDA asked the applicant to provide an appropriate caution statement regarding hepatic function monitoring in the package insert, and to continue collecting information on the incidence of hepatic dysfunction via the post-marketing surveillance.

The applicant responded that a caution statement regarding hepatic dysfunction would be provided in the "Clinically Significant Adverse Reactions" section of the package insert, that hepatic function monitoring on a regular basis would be advised, and that the incidence of hepatic dysfunction would be monitored in the post-marketing surveillance.

PMDA accepted the applicant's response.

(2).2) Cutaneous adverse events

Given that cutaneous adverse events include cases of serious erythema multiforme, and that cutaneous adverse drug reactions have been reported and cautioned against drugs in the same class, PMDA considers that collection of information on cutaneous adverse events should be continued via the post-marketing surveillance. It is also appropriate to provide a caution for cutaneous adverse events as clinically significant adverse drug reactions in the package insert: the same precaution that was taken for Feburic tablets, a drug in the same class. The above conclusion by PMDA was supported by the expert advisors. Based on the above, PMDA asked the applicant to include in the package insert an appropriate caution statement regarding the possible occurrence of cutaneous adverse events and to continue collecting information on cutaneous adverse events via the post-marketing surveillance.

The applicant responded that a caution statement regarding the possible occurrence of cutaneous adverse events would be provided in the "Clinically Significant Adverse Reactions" section of the package insert, and the incidence of cutaneous adverse events would be monitored in the post-marketing surveillance.

PMDA accepted the applicant's response.

(3) Indications

The Japanese clinical studies of topiroxostat were conducted in patients with hyperuricaemia including gout, and similar efficacy has been demonstrated irrespective of different clinical diagnosis (gout vs. hyperuricaemia). In addition, the Japanese guideline recommends treatment of hyperuricaemia aimed at preventing the onset of gout arthritis as an indication for antihyperuricaemic treatment. Based on the above, PMDA saw no problem in selecting "gout and hyperuricaemia" as the indications for the drug product. This conclusion by PMDA was supported by the expert advisors.

(4) Dosage and administration

PMDA saw no problem in selecting 60 mg twice daily as the usual maintenance dose, with possible dose increase to 80 mg twice daily in cases where the initial dose has an insufficient effect. PMDA also considered it appropriate to recommend a 2-step dose escalation procedure in the "Precautions for Dosage and Administration" section in order to reduce the incidence of gout arthritis in the early phase of treatment with topiroxostat. In addition, PMDA considered that the descriptions in the "Dosage and

Administration" and "Precautions for Dosage and Administration" sections should be modified as shown below. The above conclusion by PMDA was supported by the expert advisors. Based on the above, PMDA asked the applicant to modify the "Dosage and Administration" and "Precautions for Dosage and Administration" sections as follows. The applicant agreed with the modifications in its response, and PMDA accepted the response.

(After modification)
[Dosage and Administration]
The usual adult initial dosage is 20 mg/dose of topiroxostat orally administered twice daily in the morning and evening. Thereafter, the dose should be gradually increased, as needed, while monitoring blood uric acid levels. The usual maintenance dosage should be 60 mg/dose twice daily. The dose may be adjusted according to the patient's condition, up to 80 mg/dose twice daily.

[Precautions for Dosage and Administration]
During the early phase of antihyperuricemic treatment, gout arthritis (gout attack) may be induced by a rapid drop in blood uric acid level. Therefore, treatment with topiroxostat should be started at 20 mg/dose twice daily, and the dose should be increased gradually, for example, to 40 mg/dose twice daily at or after Week 2, and then to 60 mg/dose twice daily at or after Week 6 [see "Clinical Studies"]. The patient should be adequately monitored after dose increase.

(5) Post-marketing surveillance

PMDA considered that, during the drug use-results survey (planned number of patients, 3000; observation period, 54 weeks) aimed at studying the safety and efficacy of topiroxostat in long-term clinical use, it is necessary to collect safety information on gout arthritis, hepatic impairment, kidney- or bladder-related adverse events, cutaneous adverse events etc. as well as in patients with renal or hepatic impairment and elderly or female patients. This conclusion by PMDA was supported by the expert advisors. Based on the above, PMDA asked the applicant to present a post-marketing surveillance plan.

The applicant responded as follows:
Information on gout arthritis, hepatic impairment, kidney- or bladder-related adverse events, cutaneous adverse events, etc. will be collected during the drug use-results survey (planned number of patients, 3000; observation period, 54 weeks). The onset and outcome of gout arthritis will be recorded, and the information on the time course of serum uric acid levels, the details of dose escalation of topiroxostat, and concomitant drugs will be collected. The safety and efficacy in elderly patients and patients with renal or hepatic impairment will be investigated by extracting relevant patients. Information on efficacy and safety in female patients will also be collected.

PMDA accepted the applicant's response.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. The results showed that the design of the electronic data processing system used by the sponsor did not allow investigators to check some of the changes and revisions to the data entered early in the case report form in 5.3.5.1-2, 5.3.5.1-4, 5.3.5.1-5, and 5.3.5.1-6; and did not accommodate entry of explanations for these changes and revisions in 5.3.5.1-2, 5.3.5.1-3, 5.3.5.1-4, 5.3.5.1-5, and 5.3.5.1-6. Despite the above findings that need to be improved, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents, on the grounds that the investigators inspected the final data in the case report form and verified its contents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1-1, 5.3.5.1-3, 5.3.5.1-4, 5.3.5.1-5, 5.3.5.1-6, 5.3.5.1-7). The results identified the following findings at some clinical trial sites: protocol deviations (e.g. use of prohibited concomitant medications and noncompliance to laboratory test specifications) and entry of invalid values in the case report form. Despite the above findings that need to be improved, PMDA acknowledged overall GCP compliance in the conduct of clinical studies because the subjects in question were handled appropriately, and concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

As a result of its regulatory review, PMDA has concluded that the drug product may be approved for the following indication and dosage and administration. The re-examination period is 8 years, neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug, and the product is not classified as a biological product or a specified biological product.

[Indication]	Gout, hyperuricaemia
[Dosage and administration]	The usual adult initial dosage is 20 mg/dose of topiroxostat orally administered twice daily in the morning and evening. Thereafter, the dose should be gradually increased, as needed, while monitoring blood uric acid levels. The usual maintenance dosage should be 60 mg/dose twice daily. The dose may be adjusted according to the patient's condition, up to 80 mg/dose twice daily.