1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	FYU-981-J086-301
Study Protocol Title:	A Randomized, Multicenter, Double-Blind, Superiority Study of Dotinurad (4 mg) and Febuxostat (40 mg) for the Treatment of Subjects With Gout
Sponsor:	Eisai Co., Ltd. 4-6-10 Koishikawa, Bunkyo-Ku, Tokyo 112 8088, Japan
Applicant	FUJI YAKUHIN CO., LTD. 4-383 Sakuragi-Cho, Omiya-Ku, Saitama-Shi, Saitama 330 9508, Japan
Sponsor's Investigational Product Name:	FYU-981/dotinurad
Indication:	Gout
Phase:	3
Approval Date:	V1.0 23 Dec 2020 (Original Protocol) V2.0 03 Mar 2021 (Amendment 01) V3.0 07 Jul 2021 (Amendment 02)
GCP Statement:	This study is to be performed in full compliance with China Good Clinical Practice (C-GCP) and all applicable regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No. FYU-981
Name of Active Ingredient: Dotinurad
Study Protocol Title A Randomized, Multicenter, Double-Blind, Superiority Study of Dotinurad (4 mg) and Febuxostat (40 mg) for the Treatment of Subjects With Gout
Sites Approximately 30 sites
Study Period and Phase of Development Approximately 21 months from first subject enrolled to last subject's last visit/last assessment. Phase 3
Objectives **Primary Objective** To confirm the superiority of dotinurad 4 mg to febuxostat 40 mg on the proportion of subjects achieving a serum uric acid (SUA) level ≤6.0 mg/dL at Week 24 in Chinese subjects with gout. **Secondary Objectives** • To confirm the non-inferiority of dotinurad 2 mg to febuxostat 40 mg on the proportion of subjects achieving a SUA level ≤6.0 mg/dL at Week 12 in Chinese subjects with gout • To compare the proportion of subjects achieving a SUA level ≤6.0 mg/dL at each time point between treatment groups • To compare the percent reduction in SUA level from baseline at each time point between treatment groups • To compare the change in SUA level from baseline at each time point between treatment groups • To compare the SUA level at each time point between treatment groups • To evaluate the safety and tolerability of dotinurad

Study Design

FYU-981-J086-301 is a multicenter, randomized, double-blind, superiority, parallel-group study designed to confirm if the efficacy of dotinurad (4 mg/day) is superior to febuxostat (40 mg/day) in Chinese subjects 18 years or older in gout. Approximately 450 subjects will be randomized to treatment groups in a ratio of 1:1 and will receive dotinurad 1 mg/day for the first 4 weeks, 2 mg/day for 8 weeks, and 4 mg/day for 12 weeks; or febuxostat 20 mg/day for the first 4 weeks, and 40 mg/day for 20 weeks. In addition, the randomization will be stratified by SUA level category (<9; 9 to <10; 10 to <11; ≥11 mg/dL) and body mass index (BMI) category (<25; ≥25 kg/m^2).

The study has 3 phases: Screening Phase (4 to 28 days), Treatment I Phase (4 weeks), and Treatment II Phase (20 weeks).

Screening Phase

Screening Phase begins no more than 28 days, and no less than 4 days before the subject is randomized. During this period, informed consent will be obtained, and the subject's eligibility will be assessed.

Treatment I Phase

On Day 0 of the Treatment I Phase, subjects who meet all the inclusion criteria and none of the exclusion criteria will be randomized to 1 of 2 treatment groups (dotinurad or febuxostat).

From Day 1 of the Treatment I Phase, subjects will receive dotinurad 1 mg/day or febuxostat 20 mg/day once daily for 4 weeks.

Treatment II Phase

During the Treatment II Phase, subjects in the dotinurad group will take dotinurad 2 mg/day once daily for 8 weeks initially and 4 mg/day once daily for 12 weeks. Subjects in the febuxostat group will take febuxostat 40 mg/day once daily for 20 weeks.

Number of Subjects

Approximately 650 subjects will be screened to provide 450 randomized subjects.

Inclusion Criteria

1. Gout[a] patient (with a history of gout attack or concurrent gouty tophi) with SUA level >7.0 mg/dL in the Screening Phase (within 14 days prior to randomization)
   a: Met 2015 ACR/EULAR gout classification criteria
2. Male or female, age ≥18 years at the time of informed consent
3. Provided written informed consent signed by the subject prior to entering the study or undergoing any study procedures, indicating that they understand the purpose and procedures required for the study and are willing to participate in the study.

Exclusion Criteria

1. Females who are breastfeeding or pregnant at screening (as documented by a positive beta-human chorionic gonadotropin [β-hCG] test)
2. Females of childbearing potential who:
   - Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
     - total abstinence (if it is their preferred and usual lifestyle)
     - an intrauterine device or intrauterine hormone-releasing system (IUS)
     - a contraceptive implant
     - an oral contraceptive (Subject must have been on a stable dose of the same oral contraceptive product for at least 28 days before dosing and must agree to stay on the same dose of the oral contraceptive throughout the study and for 28 days after study drug discontinuation.)
     - have a vasectomized partner with confirmed azoospermia.
   - Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

   It is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as latex or synthetic condom plus diaphragm or cervical/vault cap with spermicide.

   NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing).
3. Patient with gouty arthritis that has not resolved within 14 days prior to randomization
4. Any history of a medical or psychiatric condition that, in the opinion of the investigator, may have affected the subject's safety or interfered with the study assessments
5. Currently has secondary hyperuricemia:
   1) Lesch-Nyhan syndrome
   2) Phosphoribosylpyrophosphate synthetase superactivity
   3) Congenital myogenic hyperuricemia
   4) Hematopoietic neoplasms (acute leukemia, lymphoma malignant, myeloproliferative disorder, myelodysplastic syndrome, etc)
   5) Solid tumors (breast cancer, seminoma, sarcoma, Wilms tumor, small cell lung cancer, etc)
   6) Non-neoplastic diseases (psoriasis vulgaris, secondary polycythemia, hemolytic anemia)
   7) Rhabdomyolysis
   8) Hypothyroidism
   9) Polycystic kidney
   10) Lead poisoning/lead nephropathy
   11) Down's syndrome
   12) Familial juvenile gouty nephropathy
   13) Hyperlactacidemia
   14) Glycogen storage disease type 1

6. A prolonged QTcF interval (QTcF >450 ms) as demonstrated by a repeated 12-lead electrocardiogram (ECG)
7. Prohibited concomitant drugs within 14 days prior to screening and during the study
8. Changing the dosage and/or administration, or initiating any restricted concomitant drugs within 14 days prior to screening and during the study
9. Have been routinely receiving non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids (not including topical application) for a disease other than gouty arthritis
10. Comorbidities with nephrolithiasis or clinical urinary calculi (eg, haematuria, back pain)
11. Evidence of clinically significant disease (eg, cardiac disease: heart failure and angina unstable, respiratory, gastrointestinal, renal, or neurological disease: cerebral infarction) that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments
12. Relevant history of cardiac (eg, myocardial infarction or angina attacks) or neurologic disease (eg, cerebral infarction) within 1 year prior to screening
13. Current presence of active gastrointestinal ulcer disease, or history of active gastrointestinal ulcer disease within 1 year prior to screening
14. Evidence of clinical significant hepatic disease: refer to Grade 2 in the "Seriousness Grading Criteria for Adverse Drug Reactions" or AST (GOT) or ALT (GPT) >3× upper limit of normal (ULN) in the Screening Phase
15. Estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73 m^2 in the Screening Phase
16. Systolic blood pressure of ≥180 mmHg or diastolic blood pressure of ≥110 mmHg in the Screening Phase
17. HbA_{1c} (NGSP value) of ≥8.4% in the Screening Phase
18. Current presence or history of neoplasm malignant in the 5 years prior to screening
19. Hypersensitivity to the study drugs (dotinurad or febuxostat) or their excipients, or all of urine alkalinizer (potassium citrate/sodium citrate hydrate compound preparations, et al)
20. Any history of or concomitant medical condition that in the opinion of the investigator(s) would compromise the subject's ability to safely complete the study
21. Scheduled for surgery during the study
22. Known to be human immunodeficiency virus (HIV) positive
23. Active viral hepatitis (B or C) as demonstrated by positive serology
24. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive or had a close contact with SARS-CoV-2 positive patient in the Screening Phase
25. Pulmonary lymphangitic involvement that results in pulmonary dysfunction requiring active treatment, including the use of oxygen
26. Use of illegal recreational drugs
27. History of drug or alcohol dependency or abuse within approximately 2 years prior to screening
28. Currently enrolled in another clinical study or used any investigational drug or device within 28 days or 5× the half-life, whichever is longer, preceding informed consent

Study Treatments

Dose Levels

	Treatment I Phase (4 weeks)	Treatment II Phase (20 weeks)	
	Day 1 to Day 28	Day 29 to Day 84 (8 weeks)	Day 85 to Day 168 (12 weeks)
Test treatment	One dotinurad 1 mg tablet and one febuxostat 20 mg-matched placebo tablet	One dotinurad 2 mg tablet and two febuxostat 20 mg-matched placebo tablets	Two dotinurad 2 mg tablets and two febuxostat 20 mg-matched placebo tablets
Comparator treatment	One febuxostat 20 mg tablet and one dotinurad 1 mg-matched placebo tablet	Two febuxostat 20 mg tablets and one dotinurad 2 mg-matched placebo tablet	Two febuxostat 20 mg tablets and two dotinurad 2 mg-matched placebo tablets

Formulation

Dotinurad will be supplied as 1 and 2 mg tablets; febuxostat-placebo will be supplied as 20 mg-matched tablet.

Febuxostat will be supplied as 20 mg tablet; dotinurad-placebo will be supplied as 1 and 2 mg-matched tablets.

Mode of Administration

The study drug will be administered orally once daily at approximately the same time each day.

Duration of Treatment

Twenty-four weeks: 4 weeks of Treatment I Phase, and 20 weeks of Treatment II Phase.

Concomitant Drug/Therapy

Prohibited Concomitant Drug and Therapy

Following drugs are prohibited within 14 days prior to screening and during the study.

1. Drugs to treat gout and hyperuricemia
   1) Uricosuric drugs (probenecid, bucolome, benzbromarone)
   2) Uric acid production-inhibitory drugs (allopurinol, febuxostat [except the investigational product])
   3) Prophylaxis for gout flare (that includes colchicine, NSAIDs, corticosteroids, et al; and does not include topical application)
2. Drugs that affect the SUA level
   1) Salicylic acid-based antipyretics and analgesics (except aspirin taken to control thromboembolism formation, and salicylamide)
3. Drugs that potentially interact with the test drug
   1) Mercaptopurine hydrate
   2) Azathioprine
   3) Vidarabine
   4) Hexamine

If a medication (including in Chinese traditional medicine) is not on the list of prohibited medications but in the opinion of the investigator, which also can be used to treat gout/hyperuricemia, it must not be used throughout the study. If a medication is not specified as prohibited but is in the same class as a medication that is listed in the protocol, and if the investigator is uncertain, the Medical Monitor must be consulted. If a subject starts any prohibited medication or therapy during the study, he/she must discontinue from the study, with the exception that certain prohibited medications must be used to particular condition if this is agreed with the Medical Monitor.

Restricted Concomitant Drug and Therapy

Subjects who are on the following treatment are required to be on a stable dose and same mode of administration for at least 14 days prior to screening and to keep the stable during the study. Subjects are not permitted to initiate these drugs within 14 days prior to screening and during the study.

1. Dietary and physical therapy for the underlying disease
2. Drugs or containing compound preparations that potentially affect SUA level
    1) Immunosuppressants (mizoribine, cyclosporin, tacrolimus hydrate)
    2) Antituberculous drugs (pyrazinamide, ethambutol hydrochloride)
    3) Hyperlipidemia drugs (fenofibrate, atorvastatin, rosuvastatin, pitavastatin)
    4) Antihypertensives (losartan potassium)
    5) Diuretics (thiazide diuretics, loop diuretics)
    6) Sodium-dependent glucose transporter (SGLT) 2 inhibitors
    7) Niacin formulations (niacin, niacinamide, tocopherol nicotinate)
    8) Theophylline
    9) Aspirin (for controlling thromboembolism formation)

Assessments

Efficacy Assessment

SUA level.

Pharmacokinetic Assessments

Not applicable.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Not applicable.

Safety Assessments

Safety assessments will consist of monitoring and recording all adverse events (AEs), and serious adverse events (SAEs); withdrawal from treatment; laboratory evaluation for hematology, blood chemistry, and urine values; periodic measurement of vital signs and ECGs; and the performance of physical examinations.

Other Assessments

Not applicable.

Bioanalytical Methods

Not applicable.

Statistical Methods

Study Endpoints

Primary Endpoint

Proportion of subjects with ≤6.0 mg/dL in SUA level at Week 24 (LOCF)

Secondary Endpoints

- Proportion of subjects with ≤6.0 mg/dL in SUA level at Week 12 (LOCF)
- Proportion of subjects with ≤6.0 mg/dL in SUA level at each time point
- Mean percent reduction from baseline in SUA level at each time point
- Mean change from baseline in SUA level at each time point
- Mean SUA level at each time point

Analysis Sets

- The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who received at least 1 dose of study drug and had at least 1 postdose primary efficacy measurement (ie, SUA level).
- The Per Protocol (PP) Analysis Set is the group of subjects who sufficiently complied with the protocol. Details of the evaluability criteria will be determined before database lock and treatment unblinding and will be specified in the statistical analysis plan (SAP).

Efficacy Analyses

The FAS will be used as a primary analysis set for the efficacy analyses.

Primary Efficacy Analysis

The analysis for the difference in the proportion of subjects with ≤6.0 mg/dL in SUA level (ie, responder rate) at Week 24 (LOCF) between dotinurad 4 mg and febuxostat 40 mg will be conducted based on a Cochran–Mantel–Haenszel (CMH) test stratified by baseline SUA level and baseline BMI. The statistical test will be two-sided at the 5% significance level.

The same primary efficacy analysis mentioned above will be repeated based on the PP Analysis Set as a sensitivity analysis.

Secondary Efficacy Analyses

For all the secondary efficacy analyses, no multiplicity adjustment will be made.

The difference in the responder rate at Week 12 (LOCF) between dotinurad 2 mg and febuxostat 40 mg and the 95% confidence interval will be estimated based on Mantel–Haenszel method adjusting for the baseline SUA level and baseline BMI. The prespecified non-inferiority margin will be –10% in this analysis, which will be for the reference purpose only.

The proportion of subjects with ≤6.0 mg/dL in SUA level at each time point will be summarized.

The mean percent reduction from baseline in SUA level at each time point will be summarized using descriptive summary statistics (eg, n, mean, SD, median, minimum, maximum), estimated based on the longitudinal data analysis (LDA) model and presented in figures. The detail of the LDA model will be specified in the SAP.

The mean actual value and the mean change from baseline in SUA level at each time point will be summarized using descriptive summary statistics.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Not applicable.

Pharmacokinetic Analyses

Not applicable.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Not applicable.

Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out of normal range laboratory safety test variables, abnormal ECG findings, out-of-normal range vital signs and weight, along with change from baseline in laboratory safety test variables, ECGs, and vital signs and weight measurements, will be summarized by treatment group using descriptive statistics.

Interim Analyses

Not applicable.

Sample Size Rationale

For the responder rate, assuming a rate of 45% for febuxostat 40 mg and 60% for dotinurad 4 mg, a sample size of 225 subjects in each group will provide approximately 90% power to detect a between-group difference in the proportion of responders based on a two-group Chi-square test with a 0.05 two-sided significance level. The primary efficacy analysis will be based on the FAS. Hence, 450 subjects will be the target number of subjects as the FAS.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ACR	American College of Rheumatology
AE	adverse event
AKI	acute kidney injury
ALT	alanine aminotransferase
AMG	alpha 1-microglobulin
AST	aspartate aminotransferase
BMG	beta 2-microglobulin
BMI	body mass index
BP	blood pressure
C-GCP	China Good Clinical Practice
CHD	coronary heart disease
CHMP	Committee for Medicinal Products for Human Use
CMH	Cochran–Mantel–Haenszel
CRA	clinical research associate/ Chinese Rheumatology Association
CRF	case report form
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CVD	cardiovascular disease
CYP	cytochrome P450
DECT	dual-energy computed tomography
ECG	electrocardiogram
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ET	early termination
EULAR	European League Against Rheumatology
FAS	Full Analysis Set
FE_{UA}	fractional excretion of urate clearance

Abbreviation	Term
FT3	free triiodothyronine
FT4	free thyroxine
GCP	Good Clinical Practice
GOT	glutamic oxaloacetic transaminase
GPT	glutamic pyruvic transaminase
HbA_{1c}	hemoglobin A1c
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDL	high density lipoprotein
HIV	human immunodeficiency virus
ICF	informed consent form
ID	identification
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IRB	Institutional Review Board
IUS	intrauterine hormone-releasing system
IxRS	interactive voice and web response system
KDIGO	Kidney Disease: Improving Global Outcomes
KOL	key opinion leader
LDA	longitudinal data analysis
LDL	low density lipoprotein
LLN	lower limit of normal
LLT	lower level term
LNH	low/normal/high
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MOA	mode of action
MSU	monosodium urate monohydrate
NAG	N-acetyl-β-D-glucosaminidase

Abbreviation	Term
NGSP	National Glycohemoglobin Standardization Program
NSAID	non-steroidal anti-inflammatory drug
PP	Per Protocol
PT	preferred term
QTcF	QT interval corrected for heart rate by Fridericia's formula
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCr	serum creatinine
SD	standard deviation
SGLT	sodium-dependent glucose transporter
SI	Système International
SOC	system organ class
SOP	standard operating procedure
SUA	serum uric acid
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory value
TSH	thyroid stimulating hormone
TT3	total triiodothyronine
TT4	total thyroxine
ULN	upper limit of normal
ULT	urate lowering treatment
URAT1	urate transporter 1
UUE	urinary urate excretion
WBC	white blood cell
WHO DD	World Health Organization Drug Dictionary

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with China Good Clinical Practice (C-GCP), and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associates [CRAs], change of telephone number[s]). Documentation of IRB/IEC compliance with C-GCP and any local regulations regarding constitution and review conduct will be provided to the sponsor.

Documented study approval from the IRB/IEC chairman must be sent to the principal investigator with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee. If the IRB/IEC decides to suspend or terminate the study, the investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable adverse events (AEs) per applicable guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki
- C-GCP
- Other applicable local regulations

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator (or designee) must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records as well as contact information

(phone number[s] of investigational site and name[s] of contact person). Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject, and after the subject has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF at screening before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with C-GCP, and all applicable local regulations. Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor (or designee) and kept on file according to local procedures at the site.

The subject should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 30 investigational sites in China.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organizations (CROs) are listed in the Investigator Study File provided to each site.

7 INTRODUCTION

7.1 Compound Overview

7.1.1 Gout

Gout is caused by hyperuricemia which is defined as a serum uric acid (SUA) concentration greater than 7.0 mg/dL. At SUA levels greater than 7.0 mg/dL, uric acid crystals can precipitate out of solution and deposit in joints and other body tissues where they can produce an inflammatory response.

In China, there has been a continuing increase in gout patients in the recent years due to changing of dietary behavior, the prolongation of life span and the continuous improvement of health care. The prevalence of gout in China has been increasing rapidly during the past years (Multi-Disciplinary Expert Task Force on Hyperuricemia and Its Related Diseases, 2017). From meta analysis, the prevalence of gout is about 1.1% (Liu, et al., 2015). Gout has become the most common arthritis related to rheumatic disease of adult. Gout is generally thought as an independent risk factor for chronic kidney disease, hypertension, coronary heart disease (CHD), cardiovascular disease (CVD) and type 2 diabetes; and an independent predictor factor for premature death (Bardin and Richett, 2017). Gout stone can cause the joint deformity, gouty nephropathy, disability, even the death.

Management of hyperuricemia at an appropriate level is important for preventing acute gouty arthritis, gouty kidney, and urinary calculi. In addition, it may protect renal function, and reduce the risks of cardiovascular disorders (Siu, et al., 2006; Athyros, et al., 2004). Based on the findings above, it is thought that urate lowering treatment (ULT) will become much more important in the future.

7.1.1.1 Current Treatment and Unmet Medical Needs

The etiology of hyperuricemia includes excessive production of uric acid, decreased excretion of uric acid, and the combined type. Approximately 90% of hyperuricemia is the uric acid decreased excretion type and the combined type in China (Chen, 2006).

The basic principle of selecting drug is based on classification of hyperuricemia. The xanthine oxidase inhibitor allopurinol has been used as a uric acid production inhibitor for many years; febuxostat is marketed later, and has been increasingly prescribed in recent years, but hepatic dysfunction, the incidence of cardiovascular death and all-cause mortality was reported to be high. Benzbromarone is the main uricosuric drug, but it can cause serious hepatic disorders (Van der Klauw, et al., 1994). It also has a potent inhibitory effect on the drug metabolizing enzyme cytochrome P450 (CYP), particularly on CYP2C9 (Kunishima, et al., 2003; Locuson, et al., 2003). So a potent, well-tolerated, and selective uricosuric drug without causing hepatic impairment, and less drug-drug interaction is needed in clinical practice.

7.1.2 Dotinurad

Fuji Yakuhin Co., Ltd. has conducted an intensive investigation on a novel uricosuric drug, and discovered dotinurad, which has a superior uricosuric effect derived from potent suppression of uric acid reabsorption.

Dotinurad reduces SUA levels by selectively inhibiting urate transporter 1 (URAT1), which is expressed on the proximal renal tubules and is responsible for reabsorption of uric acid.

7.2 Clinical Experience

The efficacy and safety of dotinurad were demonstrated in nonclinical studies and clinical studies. A total of 17 clinical studies for dotinurad were conducted in Japan, and dotinurad was approved for hyperuricemia and gout in Japan in January 2020. As for details on the results of these clinical studies for dotinurad, refer to the Investigator's Brochure.

7.3 Study Rationale

7.3.1 Targeting Population

For every gout patient, ULT should be considered and discussed. Appropriate ULT reduces the frequency of gout flare and avoids their reoccurrence. In addition, effective ULT reduces the size and number of tophi, therefor improving the quality of life of patients with gout. And it may protect renal function, and reduce the risks of cardiovascular disorders. So, ULT is recommended by the guidelines of ACR (American College of Rheumatology), EULAR (European League Against Rheumatology) and CRA (Chinese Rheumatology Association). Gout patients with SUA >7 mg/dL and a history of gout attack or concurrent gout tophi will be enrolled.

7.3.2 Primary Endpoint

The target SUA level of ≤6 mg/dL is appropriate for the most of gout patients from the guideline. It is believed that SUA level ≤6 mg/dL allows dissolution of the crystals of urate, and maintain ≤6 mg/dL also can avoid new formation of urate crystals. European Medicines Agency (EMA) paper on guideline on clinical investigation of medicinal products for the treatment of gout (EMA/CHMP/774470/2018) suggests: for confirmatory trials, the primary endpoint should be defined as sustained SUA levels below a target level of 6 mg/dL, for a period of 3 consecutive months, which starts once the treatment is optimized and stable. And guideline for the diagnosis and management of hyperuricemia and gout in China (2019) also suggests to modify the dose based on patient's SUA level for achieving the target of SUA ≤6 mg/dL (Chinese Society of Endocrinology, Chinese Medical Association, 2020). Therefore, the proportion of subjects achieving a SUA level ≤6.0 mg/dL was selected for primary endpoint.

7.3.3 Study Duration

Treatment I Phase of 4 weeks is selected to prevent the risk of gouty arthritis caused by a rapid decrease in the SUA level. The duration is based on Japan Phase 3 studies.

Eight-week duration of dotinurad 2 mg/day in Treatment II Phase is based on FYU-981-014 study, which was a Phase 3 study conducted in Japan. In FYU-981-014 study, the duration of 2 mg/day was 8 weeks. And it is sufficiently long for this duration to assess non-inferiority of dotinurad 2 mg and febuxostat 40 mg in Chinese patients. That allows us to compare Chinese data and Japanese data as necessary.

Twelve-week duration of dotinurad 4 mg/day in Treatment II Phase is based on EMA paper on guideline on clinical investigation of medicinal products for the treatment of gout (EMA/CHMP/774470/2018). According to this guideline, the pivotal trials should be sufficiently long to establish a sustained effect of urate lowering for at least 3 months, once the treatment is optimized at a stable dose level. So in this study, 12 weeks of dotinurad 4 mg/day is established.

EMA paper on guideline on clinical investigation of medicinal products for the treatment of gout also suggests that a parallel, randomized, double-blind trial should be performed for a minimum of 6 months. Therefore, subjects in the dotinurad group will be treated for 24 weeks in total.

7.3.4 Dose of Dotinurad

All antihyperuricemia drugs should be started from the low dose to avoid gout attack. Even though the approved starting dose of dotinurad in Japan is 0.5 mg/day, Chinese key opinion leaders (KOLs) suggested that 0.5 mg/day is low in terms of efficacy of dotinurad and half of treatment dose (2 mg/day), ie, 1 mg/day would be appropriate for starting dose of dotinurad. Study FYU-981-014 showed that 20-mg febuxostat group had a similar reduction rate in SUA levels (33.39±9.26%) to 1-mg dotinurad group (30.53±10.16%). This result suggests that the risk of acute gout attack caused by a rapid decrease in the SUA levels with 1 mg/day dotinurad is less likely to be exceeded 20 mg/day febuxostat. The above points suggest that the incidence of gout attack at 1 mg/day is acceptable in clinical practice.

The proportion of subjects achieving SUA level ≤6.0 mg/dL at the final visit was 84.8% (84/99 subjects) and 88.0% (88/100 subjects) in the 2-mg dotinurad group and 40-mg febuxostat group, respectively in Study FYU-981-014. From the Chinese Phase 3 studies of febuxostat, the proportion of subjects achieving SUA level ≤6.0 mg/dL tends to be approximately lower than that of Japanese subjects with the same dose of drug, is around 45%. Even though the responder rate with dotinurad 2 mg/day was over 80% in Japanese subjects, 4 mg/day might be needed to achieve SUA level ≤6.0 mg/dL in Chinese subjects.

The above points suggest it is appropriate that the titration of 1 mg/day (for 4 weeks) to 2 mg/day (for 8 weeks) of dotinurad; and increase dose to 4 mg/day (for 12 weeks).

7.3.5 Choice of Comparator Drug

Dotinurad and benzbromarone have the same mode of action (MOA), both belong to uricosuric drugs. However, benzbromarone is launched decades ago, and febuxostat has been increasingly prescribed in recent years, and is taking the place of benzbromarone's share in China. Considering these, comparison data with febuxostat will be more useful for the clinical positioning of dotinurad after launched.

Dose of Febuxostat

All ULTs should be started at a low dose and then titrated upwards, to avoid and decrease the acute gout attack. "Guideline for the diagnosis and management of hyperuricemia and gout in China (2019)" recommends to start from 20 mg/day for febuxostat (Chinese Society of Endocrinology, Chinese Medical Association, 2020), and "Chinese multi-disciplinary consensus on the diagnosis and treatment of hyperuricemia and its related diseases" recommends the starting dose of 20 to 40 mg/day (Multi-Disciplinary Expert Task Force on Hyperuricemia and Its Related Diseases, 2017). Given the above, febuxostat 20 mg was selected as a starting dose.

In Phase 3 studies of febuxostat in China (CTR20150590, CTR20130132 and CTR20130048), febuxostat 40 mg was selected to assess non-inferiority compared allopurinol 300 mg, which is set as a daily dose in its package insert. One of those Phase 3 studies selected only one dose strength, febuxostat 40 mg. Considering above, febuxostat 40 mg was selected as a compared dose.

7.3.6 Mode of Administration

As no food effects were shown in FYU-981-016 study, no restriction of food intake was imposed to dotinurad in the current study. Further, Japanese package insert indicated dotinurad should be taken once daily without stating specific timing. Febuxostat, the comparator of this study, also has no restriction of food intake. Considering the above, once daily dosing of dotinurad and febuxostat was set at approximately the same time each day.

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the study is to confirm the superiority of dotinurad 4 mg to febuxostat 40 mg on the proportion of subjects achieving a SUA level ≤6.0 mg/dL at Week 24 in Chinese subjects with gout.

8.2 Secondary Objectives

The secondary objectives of the study are:

- To confirm the non-inferiority of dotinurad 2 mg to febuxostat 40 mg on the proportion of subjects achieving a SUA level ≤6.0 mg/dL at Week 12 in Chinese subjects with gout
- To compare the proportion of subjects achieving a SUA level ≤6.0 mg/dL at each time point between treatment groups
- To compare the percent reduction in SUA level from baseline at each time point between treatment groups
- To compare the change in SUA level from baseline at each time point between treatment groups
- To compare the SUA level at each time point between treatment groups
- To evaluate the safety and tolerability of dotinurad

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

FYU-981-J086-301 is a 24-week treatment, multicenter, randomized, double-blind, superiority, parallel-group study designed to confirm if the efficacy of dotinurad (4 mg/day) is superior to febuxostat (40 mg/day) in Chinese subjects 18 years or older in gout.

The study will consist of the Screening Phase (4 to 28 days), Treatment I Phase (4 weeks), and Treatment II Phase (20 weeks).

Approximately 450 subjects will be randomized to treatment groups in a ratio of 1:1 and will receive dotinurad 1 mg/day for the first 4 weeks, 2 mg/day for 8 weeks, and 4 mg/day for 12 weeks; or febuxostat 20 mg/day for the first 4 weeks, and 40 mg/day for 20 weeks. In addition, the randomization will be stratified by SUA level category (<9; 9 to <10; 10 to <11; ≥11 mg/dL) and body mass index (BMI) category (<25; ≥25 kg/m^2).

An overview of the study design is presented in Figure 1.

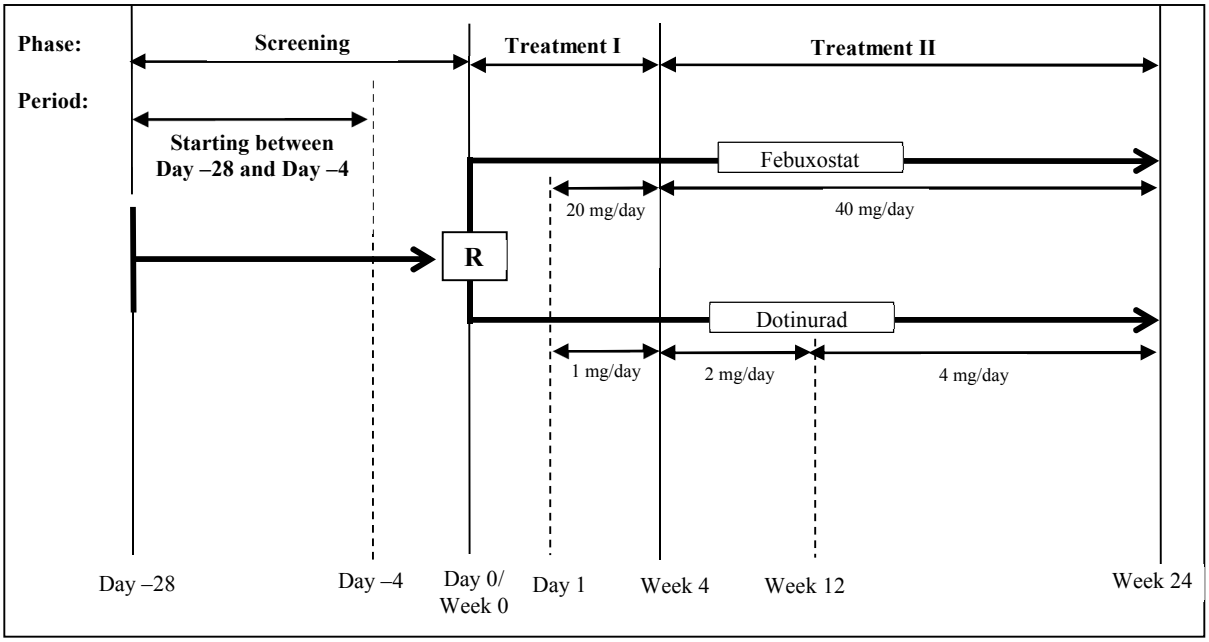


Figure 1 Overview of Study Design

R = randomization

9.1.1 Screening Phase

Screening Phase begins no more than 28 days, and no less than 4 days before the subject is randomized. Between Day –28 and Day –4, informed consent will be obtained, and the subject's eligibility will be assessed.

In the Screening Phase, medical history, demography (including other characteristics of gout/hyperuricemia), prior therapy, classification of hyperuricemia, estimated glomerular filtration rate (eGFR), serum beta-human chorionic gonadotropin (β-hCG) (or hCG) test, 12-lead ECG, abdominal ultrasound and abdominal radiography will be collected. SUA level will be assessed. Physical examinations, vital signs, safety assessments, blood and urine for standard clinical laboratory assessments also will be collected. As for the details, see Table 3.

9.1.2 Treatment I Phase

The duration of Treatment I Phase is from Week 0 (Day 0) to Week 4. On Day 0 of the Treatment I Phase, subjects who meet all the inclusion criteria and none of the exclusion criteria will be randomized to 1 of 2 treatment groups (dotinurad or febuxostat) in a ratio of 1:1.

From Day 1 of the Treatment I Phase, subjects will receive dotinurad 1 mg/day or febuxostat 20 mg/day once daily for 4 weeks.

Vital signs, concomitant therapy, safety assessments (including gouty arthritis, urinary calculi, acute renal failure, liver injury), blood and urine for standard clinical laboratory assessments will be collected at Visit 3. And SUA level will be assess at Visit 3. As for the details, see Table 3.

9.1.3 Treatment II Phase

The duration of Treatment II Phase is from the first day after Week 4 to the last day of Week 24/Early Termination Visit. During the Treatment II Phase, subjects in the dotinurad group will take dotinurad 2 mg/day once daily for 8 weeks initially and 4 mg/day once daily for 12 weeks. Subjects in the febuxostat group will take febuxostat 40 mg/day once daily for 20 weeks.

Vital signs, concomitant therapy, safety assessments (including gouty arthritis, urinary calculi, acute renal failure, liver injury), blood and urine for standard clinical laboratory assessments will be collected at each visit of Treatment II Phase. Physical examination and 12 lead ECG will be collected at Visit 5 and Visit 8. Serum β-hCG (or hCG) test, abdominal ultrasound and abdominal radiography will be collected at Visit 8. And SUA level will be assess at each visit. As for the details, see Table 3.

If a subject has any symptoms, signs, or findings about urinary calculi, acute renal failure, and severe liver injury during the whole Treatment Phase, the subject needs to have an unscheduled visit to assess the related situation.

9.2 Discussion of Study Design, Including Choice of Control Groups

Details on the rationale for the study design including the choice of comparator drug are provided in Section 7.3.

9.3 Selection of Study Population

Approximately 450 subjects will be randomized at approximately 30 sites in China. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Gout[a] patient (with a history of gout attack or concurrent gouty tophi) with SUA level >7.0 mg/dL in the Screening Phase (within 14 days prior to randomization)
   a: Met 2015 ACR/EULAR gout classification criteria
2. Male or female, age ≥18 years at the time of informed consent
3. Provided written informed consent signed by the subject prior to entering the study or undergoing any study procedures, indicating that they understand the purpose and procedures required for the study and are willing to participate in the study.

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Females who are breastfeeding or pregnant at screening (as documented by a positive β-hCG test)
2. Females of childbearing potential who:
   - Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
     - total abstinence (if it is their preferred and usual lifestyle)
     - an intrauterine device or intrauterine hormone-releasing system (IUS)
     - a contraceptive implant
     - an oral contraceptive (Subject must have been on a stable dose of the same oral contraceptive product for at least 28 days before dosing and must agree to stay on the same dose of the oral contraceptive throughout the study and for 28 days after study drug discontinuation.)
     - have a vasectomized partner with confirmed azoospermia.
   - Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

   It is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as latex or synthetic condom plus diaphragm or cervical/vault cap with spermicide.

   NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie,

bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing).

3. Patient with gouty arthritis that has not resolved within 14 days prior to randomization
4. Any history of a medical or psychiatric condition that, in the opinion of the investigator, may have affected the subject's safety or interfered with the study assessments
5. Currently has secondary hyperuricemia:
   1) Lesch-Nyhan syndrome
   2) Phosphoribosylpyrophosphate synthetase superactivity
   3) Congenital myogenic hyperuricemia
   4) Hematopoietic neoplasms (acute leukemia, lymphoma malignant, myeloproliferative disorder, myelodysplastic syndrome, etc)
   5) Solid tumors (breast cancer, seminoma, sarcoma, Wilms tumor, small cell lung cancer, etc)
   6) Non-neoplastic diseases (psoriasis vulgaris, secondary polycythemia, hemolytic anemia)
   7) Rhabdomyolysis
   8) Hypothyroidism
   9) Polycystic kidney
   10) Lead poisoning/lead nephropathy
   11) Down's syndrome
   12) Familial juvenile gouty nephropathy
   13) Hyperlactacidemia
   14) Glycogen storage disease type 1
6. A prolonged QTcF interval (QTcF >450 ms) as demonstrated by a repeated 12-lead electrocardiogram (ECG)
7. Prohibited concomitant drugs within 14 days prior to screening and during the study
8. Changing the dosage and/or administration, or initiating any restricted concomitant drugs within 14 days prior to screening and during the study
9. Have been routinely receiving non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids (not including topical application) for a disease other than gouty arthritis
10. Comorbidities with nephrolithiasis or clinical urinary calculi (eg, haematuria, back pain)
11. Evidence of clinically significant disease (eg, cardiac disease: heart failure and angina unstable, respiratory, gastrointestinal, renal, or neurological disease: cerebral infarction) that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments
12. Relevant history of cardiac (eg, myocardial infarction or angina attacks) or neurologic disease (eg, cerebral infarction) within 1 year prior to screening
13. Current presence of active gastrointestinal ulcer disease, or history of active gastrointestinal ulcer disease within 1 year prior to screening

14. Evidence of clinical significant hepatic disease: refer to Grade 2 in the "Seriousness Grading Criteria for Adverse Drug Reactions" or AST (GOT) or ALT (GPT) >3× upper limit of normal (ULN) in the Screening Phase
15. eGFR of <30 mL/min/1.73 m^2 in the Screening Phase
16. Systolic blood pressure of ≥180 mmHg or diastolic blood pressure of ≥110 mmHg in the Screening Phase
17. HbA_{1c} (NGSP value) of ≥8.4% in the Screening Phase
18. Current presence or history of neoplasm malignant in the 5 years prior to screening
19. Hypersensitivity to the study drugs (dotinurad or febuxostat) or their excipients, or all of urine alkalinizer (potassium citrate/sodium citrate hydrate compound preparations, et al)
20. Any history of or concomitant medical condition that in the opinion of the investigator(s) would compromise the subject's ability to safely complete the study
21. Scheduled for surgery during the study
22. Known to be human immunodeficiency virus (HIV) positive
23. Active viral hepatitis (B or C) as demonstrated by positive serology
24. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive or had a close contact with SARS-CoV-2 positive patient in the Screening Phase
25. Pulmonary lymphangitic involvement that results in pulmonary dysfunction requiring active treatment, including the use of oxygen
26. Use of illegal recreational drugs
27. History of drug or alcohol dependency or abuse within approximately 2 years prior to screening
28. Currently enrolled in another clinical study or used any investigational drug or device within 28 days or 5× the half-life, whichever is longer, preceding informed consent

9.3.3 Removal of Subjects From Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason (see Section 9.5.5 on the discontinuation criteria for individual subjects).

9.4 Treatments

9.4.1 Treatments Administered

The day of the first dose of study drug is defined as Day 1, ie, the first day after Visit 2 (Day 0) at which the randomization will be performed.

The following treatments will be administered to subjects in this study (Table 1).

Table 1 Treatments Administered

	Treatment I Phase (4 weeks)	Treatment II Phase (20 weeks)	
	Day 1 to Day 28	Day 29 to Day 84 (8 weeks)	Day 85 to Day 168 (12 weeks)
Test treatment	**Dotinurad 1 mg** One dotinurad 1 mg tablet and one febuxostat 20 mg-matched placebo tablet (Except Day 0)	**Dotinurad 2 mg** One dotinurad 2 mg tablet and two febuxostat 20 mg-matched placebo tablets	**Dotinurad 4 mg** Two dotinurad 2 mg tablets and two febuxostat 20 mg-matched placebo tablets
Comparator treatment	**Febuxostat 20 mg** One febuxostat 20 mg tablet and one dotinurad 1 mg-matched placebo tablet (Except Day 0)	**Febuxostat 40 mg** Two febuxostat 20 mg tablets and one dotinurad 2 mg-matched placebo tablet	**Febuxostat 40 mg** Two febuxostat 20 mg tablets and two dotinurad 2 mg-matched placebo tablets

The study drug will be administered orally once daily at approximately the same time each day.

9.4.2 Identity of Investigational Products

Investigational products, ie, test drug and active control, will be supplied by the sponsor.

Dotinurad will be supplied as 1 and 2 mg tablets; febuxostat-placebo will be supplied as 20 mg-matched tablet.

Febuxostat will be supplied as 20 mg tablet; dotinurad-placebo will be supplied as 1 and 2 mg-matched tablets.

9.4.2.1 Chemical Name of Dotinurad

- Test drug code: FYU-981
- Generic name: Dotinurad
- Chemical name: (3,5-dichloro-4-hydroxyphenyl)(1,1-dioxo-1,2-dihydro-3H-1λ^6-1,3-benzothiazol-3-yl)methanone
- Molecular formula: $C_{14}H_9Cl_2NO_4S$
- Molecular weight: 358.20
- Dosage form and content: 1 mg tablet and 2 mg tablet
- Drug Packaging: Dotinurad is packaged in blister card and paper box.
- Manufacturer: FUJI YAKUHIN CO., LTD.

9.4.2.2 Comparator Drug

- Generic name: Febuxostat
- Chemical name: 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid
- Molecular formula: $C_{16}H_{16}N_2O_3S$
- Molecular weight: 316.37
- Dosage form and content: 20 mg tablet
- Drug packaging: Febuxostat is packaged in blister card and paper box.
- Manufacturer: TEIJIN PHARMA LIMITED for febuxostat 20 mg; and Eisai Co., Ltd. for febuxostat 20 mg-matched placebo

9.4.2.3 Labeling for Study Drug

The following information has to be provided but not limited to:

- For clinical study use only
- Name of the sponsor
- Chemical name/drug identifier
- Lot number/batch number
- Storage conditions, expiration date if necessary
- Blank space for subject ID
- Blank space for site ID

9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

On Day 0 of the Treatment I Phase, subjects who meet all the inclusion criteria and none of the exclusion criteria will be randomized to 1 of 2 treatment groups (dotinurad or febuxostat) in a ratio of 1:1. In addition, the randomization will be stratified by SUA level category (<9; 9 to <10; 10 to <11; ≥11 mg/dL) and BMI category (<25; ≥25 kg/m^2).

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The

randomization scheme and identification for each subject will be included in the final clinical study report for this study.

Randomization will be performed centrally by an interactive voice and web response system (IxRS). The IxRS or clinical supply vendor will generate the randomized blister card identification numbers. At enrollment (and after successful completion of Visit 1), the investigator or designee will call the IxRS to register the subject information. At randomization (Visit 2 [Day 0]), the IxRS will assign each subject a unique randomization number.

9.4.4 Selection of Doses in the Study

Details on the doses selected for this study are provided in Section 7.3.

9.4.5 Selection and Timing of Dose for Each Subject

As stated in Section 9.4.1, the day of the first dose of study drug is defined as Day 1, ie, the first day after Visit 2 (Day 0) at which the randomization will be performed.

The study drug will be administered orally once daily at approximately the same time each day.

9.4.6 Blinding

During the Treatment I and Treatment II Phases, subjects and all personnel involved with the conduct and the interpretation of the study, including the investigators, investigational site personnel, and sponsor staff, will be blinded to the treatment codes in order to reduce potential bias during data collection and evaluation of endpoints. Randomization data will be kept strictly confidential, filed securely by an appropriate group at the sponsor or CRO, and accessible only to authorized persons per SOPs until the time of unblinding.

A master list of all treatments and the subject numbers associated with them will be maintained in a sealed envelope by the clinical supply vendor and the IxRS vendor. In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject during the study (starting at the date of informed consent) will be recorded on the case report form (CRF). The AE or medical condition for which the concomitant medication or therapy was administered will be recorded.

9.4.7.1 Prohibited Concomitant Drug and Therapy

Following drugs are prohibited within 14 days prior to screening and during the study.

1. Drugs to treat gout and hyperuricemia
   1) Uricosuric drugs (probenecid, bucolome, benzbromarone)
   2) Uric acid production-inhibitory drugs (allopurinol, febuxostat [except the investigational product])
   3) Prophylaxis for gout flare (that includes colchicine, NSAIDs, corticosteroids, et al; and does not include topical application)

2. Drugs that affect the SUA level
   1) Salicylic acid-based antipyretics and analgesics (except aspirin taken to control thromboembolism formation, and salicylamide)

3. Drugs that potentially interact with the test drug
   1) Mercaptopurine hydrate
   2) Azathioprine
   3) Vidarabine
   4) Hexamine

If a medication (including in Chinese traditional medicine) is not on the list of prohibited medications but in the opinion of the investigator, which also can be used to treat gout/hyperuricemia, it must not be used throughout the study. If a medication is not specified as prohibited but is in the same class as a medication that is listed in the protocol, and if the investigator is uncertain, the Medical Monitor must be consulted. If a subject starts any prohibited medication or therapy during the study, he/she must discontinue from the study, with the exception that certain prohibited medications must be used to particular condition if this is agreed with the Medical Monitor.

9.4.7.2 Restricted Concomitant Drug and Therapy

Subjects who are on the following treatment are required to be on a stable dose and same mode of administration for at least 14 days prior to screening and to keep the stable during the study. Subjects are not permitted to initiate these drugs within 14 days prior to screening and during the study.

1. Dietary and physical therapy for the underlying disease
2. Drugs or containing compound preparations that potentially affect SUA level
   1) Immunosuppressants (mizoribine, cyclosporin, tacrolimus hydrate)
   2) Antituberculous drugs (pyrazinamide, ethambutol hydrochloride)
   3) Hyperlipidemia drugs (fenofibrate, atorvastatin, rosuvastatin, pitavastatin)
   4) Antihypertensives (losartan potassium)
   5) Diuretics (thiazide diuretics, loop diuretics)

6) Sodium-dependent glucose transporter (SGLT) 2 inhibitors
7) Niacin formulations (niacin, niacinamide, tocopherol nicotinate)
8) Theophylline
9) Aspirin (for controlling thromboembolism formation)

9.4.7.3 Urinary Tract Management

If a subject meets any of the criteria described below, according to Guideline for the diagnosis and management of hyperuricemia and gout in China (2019): urine alkalinizer (citrate preparations, et al) must be coadministered, and keep the morning urine pH between 6.2 and 6.9. Dosage is decided on urinary pH value, generally 9 – 10 g/d for potassium sodium hydrogen citrate, and lasts for 2 – 3 months. For the specific treatment regimen (treatment targeting, drug, dosage and duration), it needs to be adjusted according to the investigator's clinical judgment based on the subject's medical situation. Even if a subject meets none of the criteria, urine alkalinizer (citrate preparations, et al) is to be coadministered as needed.

1. A history of urinary calculi
2. A urine pH of <6.0 on clinical examination after obtaining consent

9.4.7.4 Gouty Arthritis Treatment

The diagnosis of gouty arthritis can refer to Chinese version-2015 ACR/EULAR gout classification criteria, which is shown in Appendix 4 of Chinese multi-disciplinary consensus on the diagnosis and treatment of hyperuricemia and its related disease (Multi-Disciplinary Expert Task Force on Hyperuricemia and Its Related Diseases, 2017).

Subjects who have developed acute gouty arthritis attack during the study participation period are to receive pharmacologic therapy as early as possible (generally should be initiated within 24 hour of acute gout attack onset), including NSAIDs (excluding salicylic acid-based antipyretics and analgesics), colchicine, and corticosteroids. The choice of drug should be based on the presence of contraindications, the subject's previous experience with treatments, time of initiation after acute attack and the number and type of joint involved. According to Guideline for the diagnosis and management of gout in China (2016), recommended first option for acute attack is NSAIDs to relieve the symptom (1B), and then recommend to monotherapy of low dose colchicine for subjects with the contraindication of NSAIDs (2B), recommend to monotherapy of corticosteroids for the short term (2B). And from the treatment for acute gout arthritis attack, need to be adjusted according to the investigator's clinical judgment based on subjects medical situation. If a subject has developed gouty arthritis after the start of study treatment, the investigational product administration to him/her is to be continued, in principle.

<u>At Week 0/Day 0</u>
Subjects who have developed gouty arthritis attack after the randomization day and before taking the first study drug are not to receive the study drug, and the subjects are to be discontinued from the study.

At Week 4/Day 28
Subjects who have developed gouty arthritis that has not disappeared by Week 4, are to continue to take the current investigational product without increasing dose for up to 1 week after the specified visit date (ie, up to Day 35) until the event disappears, and following the resolution of event, the study drug with increasing dose is to be dispensed at an Unscheduled Visit (ie, before or on Day 35) to the recovered subject. If the gouty arthritis does not disappear by 1 week or shorter after the specified visit day (ie, within Day 35), the subject is to be discontinued from the study treatment.

At Week 12/Day 84
Subjects who have developed gouty arthritis that has not disappeared by Week 12, are to continue to take the current investigational product without increasing dose for up to 1 week after the specified visit date (ie, up to Day 91) until the event disappears, and following the resolution of event, the study drug with increasing dose is to be dispensed at an Unscheduled Visit (ie, before or on Day 91) to the recovered subject. If the gouty arthritis does not disappear by 1 week or shorter after the specified visit day (ie, within Day 91), the subject is to be discontinued from the study treatment.

At Week 24/Day 168
Subjects who have developed gouty arthritis that has not disappeared by Week 24, are to continue to take the investigational product for up to 1 week after the specified visit date (ie, up to Day 175) until the event disappears. After then, regardless of outcome of the gouty arthritis, the subjects are to undergo all procedures/assessments scheduled at Week 24.

9.4.8 Treatment Compliance

Compliance will be assessed for each study drug by examination of blister cards returned to the investigator and tablets counting at each visit and unscheduled visit. Tablets will be counted separately for tablets for dotinurad and febuxostat.

Records of treatment compliance for each subject will be kept during the study. CRAs will review treatment compliance during site visits and at the completion of the study.

9.4.9 General Precautions

The investigator will instruct subjects to be careful regarding the points listed below:

1. Subjects should avoid excessive eating and drinking during the study participation period.
2. Subjects should have sufficient water intake during the study participation period.
3. Subjects should avoid alcohol intake from the day before the study visit to the end of the study visit.
4. Subjects should avoid excessive exercise from the day before the study visit to the end of the study visit.
5. On the day of study visit, subjects should return to the investigational site without having breakfast if the visit is scheduled in the morning. If the visit is scheduled in the afternoon, subjects should visit to the investigational site without having lunch.

6. Subjects should not start other drugs during the study wherever possible. If subjects plan to use over-the-counter medications (eg, cold remedies, headache medications), they should contact the investigator before using these medications. If subjects have used these medications, they should contact the investigator on the day of study visit.
7. When subjects are planning to receive medical care by another physician, they should inform the personnel in the other site that they are receiving study treatment in this study. See also Section 9.5.7 Confirmation of Medical Care by Another Physician.
8. For females of childbearing potential, contraception by methods that are considered medically appropriate must be used during the study participation period (see Section 9.3.2 Exclusion Criteria 2).

9.4.10 Drug Supplies and Accountability

The investigator will maintain accurate records of the receipt of all study medication. In addition, accurate records will be kept regarding when and how many study medications are dispensed and used by each subject in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. Throughout the duration of the study, study medication will be reconciled on a periodic basis by the CRAs. The investigator agrees to provide sufficient access to study medication as required for the reconciliation process to be completed in a timely fashion.

At completion of the study, all study medication will be reconciled by the CRO monitor and then returned at the direction of CRO to either CRO or a third party contractor to be retained or destroyed according to applicable local regulations. Prior to any action being taken with study medication after the study is completed, the investigator will contact CRO for approval of such action.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Screening Assessments

9.5.1.1.1 DEMOGRAPHY

Subject demography information will be collected at the Screening Visit and recorded in the CRF. Demography information includes age at informed consent, sex, race/ethnicity.

9.5.1.1.2 MEDICAL HISTORY

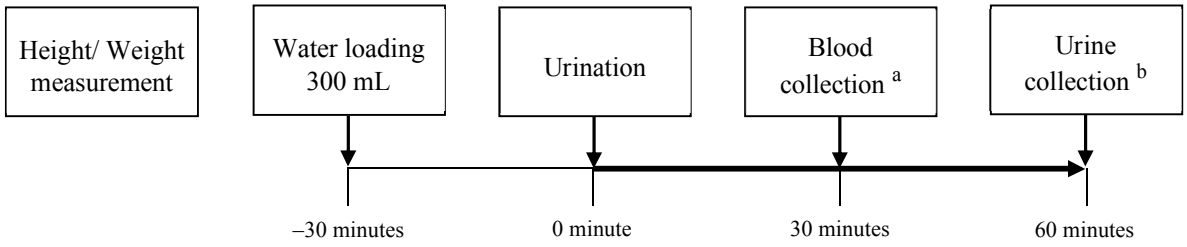
Medical and surgical history and current medical conditions will be recorded at the Screening Visit. All medical and surgical history within 5 years must be noted in the Medical History and Current Medical Conditions CRF.

9.5.1.1.3 CLASSIFICATION OF HYPERURICEMIA

The disease type of hyperuricemia will be classified according to the following methods. Height, weight, SUA level, urinary uric acid level, serum creatinine level, urinary creatinine level, and 60-minute urine volume will be measured between 14 days and 4 days before the randomization day. Urinary urate excretion (UUE; rounding off the second decimal place and displaying 1 decimal place) and fractional excretion of urate clearance (FE_{UA}; rounding off the third decimal place and displaying 2 decimal places) will be calculated and the disease type of hyperuricemia will be classified.

The measurements/calculations of height, weight, SUA level, urinary uric acid level, serum creatinine level, urinary creatinine level, 60-minute urine volume, and classification of hyperuricemia (disease type of hyperuricemia) will be recorded in the CRF. FE_{UA} and UUE will be automatically calculated and output to the CRF by the electronic data capture (EDC) system. If any parameter is considered to be reference data or unmeasurable data by the laboratory test facility or the investigator for reasons such as nonmeasurement or hemolyzed/chylous/coagulated samples, the classification of hyperuricemia is regarded as "not determination".

1. Method



a: Blood collection for SUA level and serum creatinine level measurements

b: Urine collection for urinary uric acid level, urinary creatinine level, and 60-minute urine volume measurements

2. Formulas

UUE (mg/hr/1.73 m^2):

[urinary uric acid level (mg/dL) × 60-minute urine volume (mL/hr) /100] × [1.73/body surface area (m^2) [a]]

a: Body surface area (m^2) = $weight^{0.425}$(kg) × $height^{0.725}$(cm) ×0.007184

FE_{UA} (%):

100 × [urinary uric acid level (mg/dL) × serum creatinine level (mg/dL)] / [SUA level (mg/dL) × urinary creatinine level (mg/dL)]

3. Determination of Classification of Hyperuricemia

Disease type	**UUE (mg/hr/1.73 m^2)**		**FE_{UA} (%)**
Overproduction type	>25	and	≥5.5
Underexcretion type	≤25	and	<5.5
Combined type	>25	and	<5.5

9.5.1.1.4 ESTIMATED GLOMERULAR FILTRATION RATE (eGFR)

In the Screening Phase, eGFR will be calculated at a central laboratory, and the eGFR value will be recorded in the CRF.

9.5.1.1.5 OTHER CHARACTERISTICS OF GOUT/HYPERURICEMIA

The following items on the characteristics of gout/hyperuricemia and the prior medications for gout/hyperuricemia will be surveyed at the Screening Visit and recorded in the CRF: previous urinary calculi (presence/absence), family history (presence/absence), date for the diagnosis of gout, date for the diagnosis of asymptomatic hyperuricemia, all medications used in the past for gout/hyperuricemia (none; benzbromarone; allopurinol; febuxostat; others), the last medication for gout/hyperuricemia (none; benzbromarone; allopurinol; febuxostat; others), duration of treatment for gout/hyperuricemia (none; <1; 1 to <10; ≥10 years), previous gouty arthritis (presence/absence), and previous gouty tophi (presence/absence).

9.5.1.1.6 ALCOHOL CONSUMPTION STATUS

Presence or absence of alcohol consumption will be surveyed at the Screening Visit and recorded in the CRF (when drinking frequency is at least 3 days per week and the daily regular alcohol consumption is at least 500 mL of beer, or 60 mL of whiskey, or 50 mL of low-alcohol liquor it will be taken as “presence”).

9.5.1.1.7 HEIGHT

Height without shoes will be measured at the Screening Visit and recorded in the CRF.

9.5.1.1.8 VIRAL SCREENING

Viral screening for hepatitis B (HBsAg), hepatitis C (HCV antibody IgG), and HIV will be conducted at the Screening Visit. The results will be recorded in the medical records of the site.

9.5.1.2 Efficacy Assessments

9.5.1.2.1 SERUM URIC ACID LEVEL

Efficacy assessment consists of SUA level. SUA level is considered a measure for the efficacy assessment and is not to be used in the safety assessment because there is expected to be variation in SUA level due to the pharmacological effects of dotinurad and febuxostat.

The measurement of SUA level during the study will be performed by a central laboratory. All blood samples will be collected at approximately the same time each visit, and sent to the central laboratory on the day of collection unless otherwise instructed. Laboratory certification as available will be included in the final clinical study report for this study.

Screening Phase
A blood sampling for the assessment of SUA level will be conducted between 14 days and 4 days before the randomization day. The SUA level in the Screening Phase will be recorded in the CRF (See Section 9.5.1.1.3).

The baseline is to be selected between 14 days and 4 days before, whichever is closer to the randomization day.

Treatment I and II Phases
Blood samplings for the assessment of SUA level will be conducted at approximately the same time at Weeks 4, 8, 12, 16, 20, and 24, or Early Termination Visit. The sampling date and time at each blood sampling point will be recorded in the CRF.

9.5.1.3 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker

Not applicable.

9.5.1.4 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, and serious adverse events (SAEs); withdrawal from treatment; laboratory evaluation for hematology, blood chemistry, and urine values; periodic measurement of vital signs and ECGs; and the performance of physical examinations.

9.5.1.4.1 ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drugs are dotinurad and febuxostat.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not

All AEs, regardless of relationship to study drug or procedure, should be recorded on the CRF beginning from the time the subject signs the study ICF through the last visit and for 7 days after the subject's last dose. Refer to Section 9.5.4.1 for the time period after the end of treatment for SAE collection.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF.

Abnormal ECG (QTcF) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTcF interval is more than 450 ms and there is an increase of more than 60 ms from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

All AEs must be followed for 28 days after the subject's last dose, or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the CRF. The definitions are as follows:

Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.4.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the CRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related)	A causal relationship between the study drug and the AE is a reasonable possibility.
No (not related)	A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.4.2 SERIOUS ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

9.5.1.4.3 STUDY-SPECIFIC ADVERSE EVENTS

The study-specific events, gouty arthritis, urinary calculi, acute renal failure, liver injury, should always be considered adverse events and reported on the Adverse Event CRF. As for the diagnosis of gouty arthritis, refer to Section 9.4.7.4. In addition, site(s) of onset of gouty arthritis should be collected as additional information and included in the AE term.

9.5.1.4.4 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 2. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 3) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 2 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, WBC count with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes	Calcium, chloride, potassium, sodium
Liver function tests	Alkaline phosphatase, ALT, AST, gamma glutamyl transpeptidase, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Thyroid function tests	TT3[a], FT3[a], TT4[a], FT4[a], TSH[a]
Other	Albumin, creatine kinase, globulin, glucose, HbA_{1c} (NGSP value)[a], HDL-cholesterol, lactate dehydrogenase, LDL-cholesterol, phosphorus, serum amylase, total protein, triglycerides
Urinalysis	Qualitative (protein, glucose, urobilinogen, occult blood, ketones), pH, specific gravity, urinary sediments (microscopy), NAG[b], AMG[b], BMG[b], osmolality, microalbumin[b]

ALT = alanine aminotransferase, AMG = alpha 1-microglobulin, AST = aspartate aminotransferase, BMG = beta 2-microglobulin, FT3 = free triiodothyronine, FT4 = free thyroxine, HbA_{1c} = hemoglobin A1c, HDL = high density lipoprotein, LDL = low density lipoprotein, NAG = N-acetyl-β-D-glucosaminidase, NGSP = National Glycohemoglobin Standardization Program, RBC = red blood cell, TSH = thyroid stimulating hormone, TT3 = total triiodothyronine, TT4 = total thyroxine, WBC = white blood cell.

a: Measure only in the Screening Phase.

b: Calculate with corrected urinary creatinine.

Clinical laboratory tests during the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. Laboratory certification as available will be included in the final clinical study report for this study.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.4.1). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

9.5.1.4.5 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic blood pressure [BP] [mmHg], pulse [beats per minute] and temperature [°C]), and weight (kg) will be obtained at the visits designated in the Schedule of Procedures/Assessments (Table 3) by a validated method, and the results will be recorded in the CRF.

Blood pressure and pulse will be measured after the subject has been sitting for approximately 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.

When vital signs are to be obtained concurrently with blood samples, the vital sign measurements will be performed before drawing blood samples in order to maximize the accuracy of blood sampling times while minimizing the potential effects of blood drawing on recordings obtained during safety assessments.

9.5.1.4.6 PHYSICAL EXAMINATIONS

Physical examinations will only be performed at the Screening Visit, Week 12, and Week 24/Early Termination Visit (Table 3). For all other visits during the study, the physical examinations will only be performed when there is a complaint from the subject. Documentation of the physical examination will be included in the source documentation at the site. Clinically significant abnormal findings that meet the definition of an AE from the physical examinations will be reported on the Adverse Events CRF.

9.5.1.4.7 ELECTROCARDIOGRAMS

Twelve-lead ECG will be obtained as designated in the Schedule of Procedures/Assessments (Table 3).

ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) and parameters (QTcF, QT, PR, QRS, RR and heart rate) will be recorded on the CRF. If subject has a normal ECG baseline reading, but during any visit thereafter the QTcF is measured as >450 ms, 3 consecutive ECGs, including the initial ECG with QTcF >450 ms, separated by at least 5 minutes will be performed to confirm the abnormality, and the mean of the 3 QTcF values will be recorded on the CRF.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.4.1). In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

9.5.1.4.8 OTHER SAFETY ASSESSMENTS

Pregnancy Test

A serum β-hCG (or hCG) test will be performed at the Screening Visit and Week 24/Early Termination Visit (Table 3) for premenopausal women and postmenopausal women who

have been amenorrheic for less than 12 consecutive months. The results will be recorded in the medical records of the site.

Abdominal Ultrasound/Abdominal Radiography

Abdominal ultrasound and plain abdominal radiography will be performed at the Screening Visit and Week 24/Early Termination Visit (Table 3), and the presence or absence of urinary calculi or clinically significant urinary calculi will be observed. Documentation of the abdominal ultrasound and plain abdominal radiography will be included in the source documentation at the site. Clinically significant abnormal findings that meet the definition of an AE from the abdominal ultrasound and plain abdominal radiography will be reported on the Adverse Events CRF.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 3 presents the schedule of procedures/assessments.

Table 3 Schedule of Procedures/Assessments in Study FYU-981-J086-301

Phase	Screening	Treatment I		Treatment II						
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**ET[a]**	**Unscheduled [o]**
Week	**–4**	**0[b]**	**4[c]**	**8**	**12[d]**	**16**	**20**	**24[e]**		
Day	**–28**	**0**	**28**	**56**	**84**	**112**	**140**	**168**		
Possible Study Day(s) Given Window	**–28 to –4**	**0**	**23 to 33**	**51 to 61**	**77 to 91**	**105 to 119**	**133 to 147**	**161 to 175**		
Procedures/Assessments										
Demography	X									
Informed consent/assent	X									
Inclusion/exclusion criteria	→									
Medical history	X									
Alcohol consumption status	X									
Prior and concomitant medication(s)	→								X	X
Urinary tract management[f]	X	X	X	X	X	X	X	X	X	X
Adverse events	→								X	X
Gouty arthritis	→								X	X
Randomization		X								
Study drug		Day 1 →								
Study drug compliance			X	X	X	X	X	X	X	X
Dispense study drug		X	X	X	X	X	X			X
Retrieve unused study drug			X	X	X	X	X	X	X	X
Physical examination[g]	X				X			X	X	X
Vital signs[h] and weight	X	X	X	X	X	X	X	X	X	X
Height[i]	X									

Table 3 Schedule of Procedures/Assessments in Study FYU-981-J086-301

Phase	Screening	Treatment I		Treatment II						
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**ET[a]**	**Unscheduled [o]**
Week	**–4**	**0[b]**	**4[c]**	**8**	**12[d]**	**16**	**20**	**24[e]**		
Day	**–28**	**0**	**28**	**56**	**84**	**112**	**140**	**168**		
Possible Study Day(s) Given Window	**–28 to –4**	**0**	**23 to 33**	**51 to 61**	**77 to 91**	**105 to 119**	**133 to 147**	**161 to 175**		
Procedures/Assessments										
Clinical laboratory tests[j]	X		X	X	X	X	X	X	X	X
Viral screening[k]	X									
Serum uric acid level[l]	X		X	X	X	X	X	X	X	X
Serum β-hCG (or hCG) test[m]	X							X	X	
Classification of hyperuricemia[p]	X									
eGFR	X									
12-lead ECG[n]	X				X			X	X	X
Abdominal ultrasound /abdominal radiography	X							X	X	

X: required done.

β-hCG = beta-human chorionic gonadotropin (or hCG = human chorionic gonadotropin); CRF = case report form; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ET = early termination; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; SUA = serum uric acid.

a: These assessments will be conducted for subjects who discontinued the study early for any reason after Visit 2.
b: Subjects who have developed gouty arthritis attack after the randomization day and before taking the first study drug are not to receive the study drug, and the subjects are to be discontinued from the study.
c: Subjects who have developed gouty arthritis that has not disappeared by Week 4, are to continue to take the current investigational product without increasing dose for up to 1 week after the specified visit date (ie, up to Day 35) until the event disappears, and following the resolution of event, the study drug with increasing dose is to be dispensed at an Unscheduled Visit (ie, before or on Day 35) to the recovered subject. If the gouty arthritis does not disappear by 1 week or shorter after the specified visit day (ie, within Day 35), the subject is to be discontinued from the study treatment.
d: Subjects who have developed gouty arthritis that has not disappeared by Week 12, are to continue to take the current investigational product without increasing dose for up to 1 week after the specified visit date (ie, up to Day 91) until the event disappears, and following the resolution of event, the study drug with increasing dose is to be dispensed at an Unscheduled Visit (ie, before or on Day 91) to the recovered subject. If the gouty arthritis does not disappear by 1 week or shorter after the specified visit day (ie, within Day 91), the subject is to be discontinued from the study treatment.
e: Subjects who have developed gouty arthritis that has not disappeared by Week 24, are to continue to take the investigational product for up to 1 week after the specified visit date (ie, up to Day 175) until the event disappears. After then, regardless of outcome of the gouty arthritis, the subjects are to undergo all procedures/assessments scheduled at Week 24.
f: If a subject meets any of the criteria: 1) a history of urinary calculi; 2) a urine pH of <6.0 on clinical examination after obtaining consent, urine alkalinizer (citrate preparations, et al) must be coadministered. Even if a subject meets none of the criteria, urine alkalinizer (citrate preparations, et al) is to be coadministered as needed.
g: Physical examinations will only be performed at Visit 1, Visit 5, Visit 8, and at Early Termination Visit. For all other visits during the study, the physical examinations will only be performed when there is a complaint from the subject. Clinically significant abnormal findings from the physical examinations will be reported as adverse events.
h: Vital signs include systolic and diastolic blood pressure, pulse, and temperature.
i: Height without shoes will be measured.
j: Clinical laboratory tests include hematology, blood chemistry, and urinalysis.
k: Viral screening for hepatitis B (HBsAg), hepatitis C (HCV antibody IgG), and HIV will be conducted.
l: The baseline is to be selected between 14 days and 4 day before, whichever is closer to the randomization day.
m: Female subjects only.
n: If subject has a normal ECG baseline reading, but during any visit thereafter the QTcF is measured as >450 ms, 3 consecutive ECGs, including the initial ECG with QTcF >450 ms, separated by at least 5 minutes will be performed to confirm the abnormality. ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) and parameters (QTcF, QT, PR, QRS, RR and heart rate) will be recorded on the CRF.
o: At the unscheduled visit, as for the 2 safety assessments (ie, lab tests and ECG) and SUA assessment, they will be performed only if the investigator(s) judges as necessary based on the subject's condition.
p: Height, weight, SUA level, urinary uric acid level, serum creatinine level, urinary creatinine level, and 60-minute urine volume will be measured.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of gout.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, radiologic studies, and assessment of AEs, are standard evaluations to ensure subject safety.

As stated in Section 9.5.1.2.1, SUA level is considered a measure for the efficacy assessment and is not to be used in the safety assessment because there is expected to be variation in SUA level due to the pharmacological effects of dotinurad and febuxostat.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SERIOUS ADVERSE EVENTS, regardless of their relationship to study treatment, must be reported to the designated CRO on a completed SAE form by email or fax as soon as possible but no later than 24 hours from the date the investigator becomes aware of the event.

Serious adverse events, regardless of causality assessment, must be collected beginning from the time the subject signs the study ICF through the last visit and for 28 days after the subject's last dose. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

Reporting of AEs to regulatory authorities are provided in Section 9.5.4.6.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in a female subject in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, a spontaneous abortion or an induced abortion done due to safety concerns for either mother or fetus are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of Serious Adverse Events [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 24 hours from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 24 hours from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study.

9.5.4.3 Reporting of Events Associated with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects

Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse and Intentional Overdose, even if asymptomatic, are always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

9.5.4.3.2 Reporting of Abnormal Hepatic Tests of Clinical Interest

The following combination of abnormal laboratory tests*, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing and whether nonserious or serious, should be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1). If the event does not meet serious criteria, the seriousness criteria on the SAE form should be indicated as "nonserious."

- Elevated AST or ALT lab value that is greater than or equal to 3× ULN
  AND
- Elevated total bilirubin lab value that is greater than or equal to 2× ULN
  AND AT THE SAME TIME
- Alkaline phosphatase lab value that is less than 2× ULN

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require additional evaluation for an underlying etiology. In addition to reporting the abnormal hepatic laboratory tests on an SAE form, the site should also consult the medical monitor for guidance on assessment and follow-up. At a minimum, laboratory testing should be repeated at least once weekly until improvement or identification of a cause unrelated to study drug use that is unlikely to improve.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break

will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

For this study, the Reference Safety Information which the Sponsor will use to assess expectedness is the Investigator Brochure of dotinurad/the approved China Package Insert of febuxostat.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue the study at any time for any reason. Wherever possible, all subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 3).

Subjects who meet any of the following criteria will be discontinued from the study:

1. Subjects who withdrew consent
2. Subject choice (eg, change in residence)
3. Subjects who had AEs leading to discontinuation from the study
4. Subjects who were considered impossible to continue the study due to progression of gout or inadequate therapeutic effect of the study drug by the investigator
5. Subjects who take prohibited concomitant drugs during the study, and the use is considered to interfere with the efficacy assessments and affect the subject's safety by the investigator, following consultation with the sponsor
6. Subjects who change the dosage and/or administration, or initiate any restricted concomitant drugs during the study, and the change or initiation is considered to interfere with the efficacy assessments and affect the subject's safety by the investigator, following consultation with the sponsor
7. Subjects who begin to routinely receive NSAIDs or corticosteroids (not including topical application) for a disease other than gouty arthritis
8. Subjects who developed gouty arthritis attack after the randomization day and before taking the first study drug
9. Subjects who developed gouty arthritis at Week 4 or 12, and the gouty arthritis did not disappear within 1 week after the specified visit date of Week 4 or 12
10. Subjects who developed nephrolithiasis (including clinical urinary calculi) after the first study treatment (excluding at the final visit)

11. Subjects who developed acute kidney injury (AKI) after the first study treatment (excluding at the final visit)

    AKI is defined as any of the following (Kidney Disease: Improving Global Outcomes [KDIGO] 2012):

    - Increase in serum creatinine (SCr) by ≥0.3 mg/dL (≥26.5 μmol/L) within 48 hours; or
    - Increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
    - Urine volume <0.5 mL/kg/h for 6 hours
12. Subjects with SUA level of ≤2.0 mg/dL for 2 consecutive visits (excluding at the final visit)
13. Subjects with AST or ALT level of 5× ULN (excluding at the final visit)
14. Subjects with serum creatinine level of ≥3.0 mg/dL (excluding at the final visit)
15. Subjects who became pregnant after the first study treatment
16. Subjects who were considered inappropriate to continue the study due to any other reason by the investigator

Subjects who discontinue early from the study will be discontinued for 1 primary reason of the above reasons. In addition to the primary reason, the subject may indicate 1 or more secondary reason(s) for discontinuation. Study disposition information will be collected on the Subject Disposition CRF.

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

A subject removed from the study for any reason may not be replaced. In some circumstances, a subject who fails in the Screening Phase may be rescreened once following consultation with Medical Monitor of the Sponsor. Any such subject will be assigned a new subject identification number.

9.5.6 Abuse or Diversion of Study Drug

Not applicable.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by C-GCP, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, SUA levels, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding. Statistical analyses will be performed using SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock and treatment unblinding.

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT

The primary endpoint is the proportion of subjects with ≤6.0 mg/dL in SUA level at Week 24 (LOCF).

9.7.1.1.2 SECONDARY ENDPOINTS

The secondary endpoints are:

- Proportion of subjects with ≤6.0 mg/dL in SUA level at Week 12 (LOCF)
- Proportion of subjects with ≤6.0 mg/dL in SUA level at each time point
- Mean percent reduction from baseline in SUA level at each time point
- Mean change from baseline in SUA level at each time point
- Mean SUA level at each time point

9.7.1.2 Definitions of Analysis Sets

The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment.

The Full Analysis Set (FAS) is the group of randomized subjects who received at least 1 dose of study drug and had at least 1 postdose primary efficacy measurement (ie, SUA level).

The Per Protocol (PP) Analysis Set is the group of subjects who sufficiently complied with the protocol. Details of the evaluability criteria will be determined before database lock and treatment unblinding and will be specified in the SAP.

9.7.1.3 Subject Disposition

The number of subjects screened and the number failing screening (overall and by reason for failure) will be summarized. The number of subjects randomized along with the number of subjects in each of the study populations will also be presented.

The number of subjects completing the study will be presented. Subjects who prematurely terminated their participation in the study will be summarized by their primary reason for study termination. Other reasons for study terminations will also be summarized. These tabulations will be produced for all randomized subjects by treatment group.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics in the Safety Analysis Set, FAS, and PP will be summarized for each treatment group using descriptive statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables). Continuous variables include age, height, weight, BMI; categorical variables

include sex, age group (<45; 45 to <55; 55 to <65; ≥65 years old), BMI group (<25; ≥25 kg/m^2), race, and ethnicity.

Characteristics of gout/hyperuricemia and the prior medications for gout/hyperuricemia for the Safety Analysis Set, FAS, and PP will be summarized for each treatment group using descriptive statistics. Continuous variables include SUA level and eGFR; categorical variables include all medications used in the past for gout/hyperuricemia (none; benzbromarone; allopurinol; febuxostat; others), the last medication for gout/hyperuricemia (none; benzbromarone; allopurinol; febuxostat; others), SUA level category (<9; 9 to <10; 10 to <11; ≥11 mg/dL), eGFR category (≥30 to <60; 60 to <90; ≥90 mL/min/1.73 m^2), and classification of hyperuricemia (overproduction type, underexcretion type; combined type/normal type).

Details of the statistical analyses for the demographic and other characteristics will be indicated in the SAP.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD).

Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug. In addition, prior and concomitant nonpharmacological procedures will be defined similarly to prior and concomitant medications.

All medications and nonpharmacological procedures will be presented in subject data listings.

9.7.1.6 Efficacy Analyses

The FAS will be used as a primary analysis set for the efficacy analyses.

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

The analysis for the difference in the proportion of subjects with ≤6.0 mg/dL in SUA level (ie, responder rate) at Week 24 (LOCF) between dotinurad 4 mg and febuxostat 40 mg will be conducted based on a Cochran–Mantel–Haenszel (CMH) test stratified by baseline SUA level and baseline BMI. The statistical test will be two-sided at the 5% significance level.

The same primary efficacy analysis mentioned above will be repeated based on the PP Analysis Set as a sensitivity analysis.

Subgroup analyses will be performed as appropriate.

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

For all the secondary efficacy analyses, no multiplicity adjustment will be made.

The difference in the responder rate at Week 12 (LOCF) between dotinurad 2 mg and febuxostat 40 mg and the 95% confidence interval will be estimated based on Mantel–Haenszel method adjusting for the baseline SUA level and baseline BMI. The prespecified non-inferiority margin will be –10% in this analysis, which will be for the reference purpose only.

The proportion of subjects with ≤6.0 mg/dL in SUA level at each time point will be summarized.

The mean percent reduction from baseline in SUA level at each time point will be summarized using descriptive summary statistics (eg, n, mean, SD, median, minimum, maximum), estimated based on the longitudinal data analysis (LDA) model and presented in figures. The detail of the LDA model will be specified in the SAP.

The mean actual value and the mean change from baseline in SUA level at each time point will be summarized using descriptive summary statistics.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Not applicable.

9.7.1.8 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety data, presented by treatment group, will be summarized on an "as treated" basis using descriptive statistics. Safety variables include treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital signs, weight, 12-lead ECG results.

9.7.1.8.1 EXTENT OF EXPOSURE

The duration of exposure to study drug will be summarized descriptively. The number (percentage) of subjects will also be summarized by duration of exposure.

Compliance will be assessed for each study drug by examination of blister cards returned to the investigator and tablets counting at each visit and unscheduled visit. Tablets will be counted separately for tablets for dotinurad and febuxostat (see Section 9.4.8). Summaries will provide descriptive summary statistics and number (percentage) of subjects (<80%; 80% to 100%; >100% to 120%; >120%).

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities

(MedDRA). Adverse events will be coded to the MedDRA lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during time from the first dose of study drug to 28 days after the subject's last dose, having been absent at pretreatment or

- Reemerges during treatment, having been present at pretreatment but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study treatment. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

Subgroup analyses for TEAEs will be performed as appropriate.

A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent SAEs will be summarized by SOC and PT for each treatment group. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by SOC and PT for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Section 9.5.1.4.4, the actual value and the change from baseline to each postbaseline visit will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.4.4 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value.

Appendix 1 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

9.7.1.8.4 VITAL SIGNS AND WEIGHT

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse and temperature) and weight, and changes from baseline will be presented by visit and treatment group.

The number (percentage) of subjects with at least 1 postbaseline clinically notable values in vital signs and weight will be summarized. Clinically notable values will be defined in the SAP.

9.7.1.8.5 ELECTROCARDIOGRAMS

Descriptive statistics for ECG parameters (QTcF, QT, PR, QRS, RR and heart rate) and changes from baseline will be presented by visit and treatment group.

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) by visit and treatment group.

In addition, the number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTcF will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

Absolute QTcF interval prolongation:

- QTcF interval >450 ms
- QTcF interval >480 ms
- QTcF interval >500 ms

Change from baseline in QTcF interval:

- QTcF interval increases from baseline >30 ms
- QTcF interval increases from baseline >60 ms

9.7.1.8.6 OTHER SAFETY ANALYSES

No analyses are planned for pregnancy tests, and abdominal ultrasound and plain abdominal radiography specified in Section 9.5.1.4.8 Other Safety Assessments.

9.7.2 Determination of Sample Size

For the responder rate, assuming a rate of 45% for febuxostat 40 mg and 60% for dotinurad 4 mg, a sample size of 225 subjects in each group will provide approximately 90% power to detect a between-group difference in the proportion of responders based on a two-group Chi-square test with a 0.05 two-sided significance level. The primary efficacy analysis will be based on the FAS. Hence, 450 subjects will be the target number of subjects as the FAS.

9.7.3 Interim Analysis

Not applicable.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the SAP needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

10 REFERENCE LIST

Athyros VG, Elisaf M, Papageorgiou AA, Symeonidis AN, Pehlivanidis AN, Bouloukos VI, et al. Effect of statins versus untreated dyslipidemia on serum uric acid levels in patients with coronary heart disease: a subgroup analysis of the Greek atorvastatin and coronary-heart-disease evaluation (GREACE) study. Am J Kidney Dis. 2004;43(4):589–99.

Bardin T and Richett P. Impact of comorbidities on gout and hyperuricemia: an update on prevalence and treatment options. BMC Med. 2017;15(1):123.

Chen Haozhu. Practice of internal medicine. Beijing: People's Medical Publishing House. 2006;2605.

Chinese Society of Endocrinology, Chinese Medical Association. Guideline for the diagnosis and management of hyperuricemia and gout in China (2019). Chin Endocrinol Metab. 2020;36(1):1–13.

European Medicines Agency. Guideline on clinical investigation of medicinal products for the treatment of gout. EMA/CHMP/774470/2018; 2019.

Hosoya T, Sano T, Sasaki T, Fushimi M, Ohashi T. Dotinurad versus benzbromarone in Japanese hyperuricemic patient with or without gout: a randomized, double-blind, parallel-group, phase 3 study. Clinical and Experimental Nephrology. 2020;24 (Suppl 1):S62–S70.

Kunishima C, Inoue I, Oikawa T, Katayama S. The metabolism, toxicity and pharmacological studies of benzbromarone (Urinorm®). (in Japanese) J Saitama Med School. 2003;30(4):187–94.

Liu R, Han C, Wu D, Xia X, Gu J, Guan H, et al. Prevalence of hyperuricemia and gout in mainland China from 2000 to 2014: a systematic review and meta-analysis. Biomed Res Int. 2015;2015:762820.

Locuson II CW, Wahlstrom JL, Rock DA, Rock DA, Jones JP. A new class of CYP2C9 inhibitors: probing 2C9 specificity with high-affinity benzbromarone derivatives. Drug Metab Dispos. 2003;31(7):967–71.

Multi-Disciplinary Expert Task Force on Hyperuricemia and Its Related Diseases. Chinese multi-disciplinary consensus on the diagnosis and treatment of hyperuricemia and its related diseases. Zhonghua Nei Ke Za Zhi. 2017;56(3): 235–48.

Neogi T, Jansen TL, Dalbeth N, Fransen J, Schumacher HR, Berendsen D, et al. 2015 Gout classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2015;74(10):1789–98.

Siu YP, Leung KT, Tong MKH, Kwan TH. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. Am J Kidney Dis. 2006;47(1):51–9.

Van der Klauw MM, Houtman PM, Stricker BHC, Spoelstra P. Hepatic injury caused by benzbromarone. J Hepatol. 1994;20(3):376–9.

11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor (or appropriate study team member) and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol.

11.3 Monitoring Procedures

The sponsor's/CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site and remote monitoring will be conducted by the assigned CRA as described in the monitoring plan. The investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with C-GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

Source documents include, but are not limited to the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes which have been certified for accuracy after production

- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, ECGs) regardless of how these images are stored, including microfiche and photographic negatives
- Medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents. The data recorded directly on the CRF are to be considered as source data.

The investigator is to agree to allow direct access to source documents and study facilities to sponsor representative(s), monitor(s) and auditor(s), and is to agree to inspection by regulatory authorities or IRB/IEC representative.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 15 years following the completion of the study.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of C-GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor (or designated contractor). Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA (or designated contractor) or, when approval is given by the sponsor, will destroy supplies and containers at the site.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	Life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 2.5×ULN if baseline was normal; 2.0 – 2.5×baseline if baseline was abnormal	>2.5 – 5.0×ULN if baseline was normal; >2.5 – 5.0×baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 – 20.0×baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0×baseline if baseline was abnormal
ALT	>ULN – 3.0×ULN if baseline was normal; 1.5 – 3.0×baseline if baseline was abnormal	>3.0 – 5.0×ULN if baseline was normal; >3.0 – 5.0×baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 – 20.0×baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0×baseline if baseline was abnormal
AST	>ULN – 3.0×ULN if baseline was normal; 1.5 – 3.0×baseline if baseline was abnormal	>3.0 – 5.0×ULN if baseline was normal; >3.0 – 5.0×baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 – 20.0×baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0×baseline if baseline was abnormal
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN if baseline was normal; 1.0 – 1.5×baseline if baseline was abnormal	>1.5 – 3.0×ULN if baseline was normal; >1.5 – 3.0×baseline if baseline was abnormal	>3.0 – 10.0×ULN if baseline was normal; >3.0 – 10.0×baseline if baseline was abnormal	>10.0×ULN if baseline was normal; >10.0×baseline if baseline was abnormal
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L Ionized calcium <LLN - 1.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	<6.0 mg/dL <1.5 mmol/L Ionized calcium <0.8 mmol/L; life-threatening consequences

	Grade 1	Grade 2	Grade 3	Grade 4
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L Ionized calcium >ULN - 1.5 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	>13.5 mg/dL >3.4 mmol/L Ionized calcium >1.8 mmol/L; life-threatening consequences
Creatinine	>ULN – 1.5×ULN	>1.5 - 3.0×baseline; >1.5 – 3.0×ULN	>3.0×baseline; >3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 2.5×ULN if baseline was normal; 2.0 - 2.5×baseline if baseline was abnormal	>2.5 – 5.0×ULN if baseline was normal; >2.5 - 5.0×baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 - 20.0×baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0×baseline if baseline was abnormal
Glucose, serum-high (hyperglycemia)	Abnormal glucose above baseline with no medical intervention	Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes	Insulin therapy initiated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L Life-threatening consequences; seizures
Phosphate, serum-low (hypophosphatemia)	Laboratory finding only and intervention not indicated	Oral replacement therapy indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	Life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L Life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L Life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L; intervention initiated	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L Life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	125-129 mmol/L and asymptomatic	125 – 129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms	<120 mmol/L Life-threatening consequences

	Grade 1	Grade 2	Grade 3	Grade 4
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L Life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.
Based on Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

Appendix 2 The ACR/EULAR Gout Classification Criteria (Neogi, et al., 2015)

	Categories	Score
Step 1: Entry criterion (only apply criteria below to those meeting this entry criterion)	At least 1 episode of swelling, pain, or tenderness in a peripheral joint or bursa	
Step 2: Sufficient criterion (if met, can classify as gout without applying criteria below)	Presence of MSU crystals in a symptomatic joint or bursa (ie, in synovial fluid) or tophus	
Step 3: Criteria (to be used if sufficient criterion not met)		
Clinical		
Pattern of joint/bursa involvement during symptomatic episode(s) ever [a]	Ankle or midfoot (as part of monoarticular or oligoarticular episode without involvement of the first metatarsophalangeal joint	1
	Involvement of the first metatarsophalangeal joint (as part of monoarticular or oligoarticular episode)	2
Characteristics of symptomatic episode(s) ever • Erythema overlying affected joint (patient-reported or physician-observed) • Can't bear touch or pressure to affected joint • Great difficulty with walking or inability to use affected joint	One characteristic Two characteristics Three characteristics	1 2 3
Time course of episode(s) ever Presence (ever) of ≥2, irrespective of antiinflammatory treatment: • Time to maximal pain <24 hours • Resolution of symptoms in ≤14 days • Complete resolution (to baseline level) between symptomatic episodes	One typical episode Recurrent typical episodes	1 2
Clinical evidence of tophus Draining or chalk-like subcutaneous nodule under transparent skin, often with overlying vascularity, located in typical locations: joints, ears, olecranon bursae, finger pads, tendons (eg, Achilles)	Present	4
Laboratory		
Serum urate: Measured by uricase method. Ideally should be scored at a time when the patient was not receiving urate-lowering treatment and it was >4 weeks from the start of an episode (ie, during intercritical period); *if* practicable, retest under those conditions. The highest value irrespective of timing should be scored.	<4 mg/dL (<0.24 mmoles/liter) [b] 6 – <8 mg/dL (0.36 – <0.48 mmoles/liter) 8 – <10 mg/dL (0.48 – <0.60 mmoles/liter) ≥10 mg/dL (≥0.60 mmoles/liter)	–4 2 3 4
Synovial fluid analysis of a symptomatic (ever) joint or bursa (should be assessed by a trained observer) [c]	MSU negative	–2

	Categories	Score
Imaging [d]		
Imaging evidence of urate deposition in symptomatic (ever) joint or bursa: ultrasound evidence of double-contour sign [e] *or* DECT demonstrating urate deposition [f]	Present (either modality)	4
Imaging evidence of gout-related joint damage: conventional radiography of the hands and/or feet demonstrates at least 1 erosion [g]	Present	4

A web-based calculator can be accessed at: http://goutclassificationcalculator.auckland.ac.nz, and through the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) web sites.

a: Symptomatic episodes are periods of symptoms that include any swelling, pain, and/or tenderness in a peripheral joint or bursa.

b: If serum urate level is <4 mg/dL (<0.24 mmoles/liter), *subtract 4 points*; if serum urate level is ≥4 – <6 mg/dL (≥0.24 – <0.36 mmoles/liter), score this item as 0.

c: If polarizing microscopy of synovial fluid from a symptomatic (ever) joint or bursa by a trained examiner fails to show monosodium urate monohydrate (MSU) crystals, *subtract 2 points*. If synovial fluid was not assessed, score this item as 0.

d: If imaging is not available, score these items as 0.

e: Hyperechoic irregular enhancement over the surface of the hyaline cartilage that is independent of the insonation angle of the ultrasound beam (note: false-positive double-contour sign [artifact] may appear at the cartilage surface but should disappear with a change in the insonation angle of the probe).

f: Presence of color-coded urate at articular or periarticular sites. Images should be acquired using a dual-energy computed tomography (DECT) scanner, with data acquired at 80 kV and 140 kV and analyzed using gout-specific software with a 2-material decomposition algorithm that color-codes urate. A positive scan is defined as the presence of color-coded urate at articular or periarticular sites. Nailbed, submillimeter, skin, motion, beam hardening, and vascular artifacts should not be interpreted as DECT evidence of urate deposition.

g: Erosion is defined as a cortical break with sclerotic margin and overhanging edge, excluding distal interphalangeal joints and gull wing appearance.

A threshold score of ≥8 classifies an individual as having gout.

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	FYU-981-J086-301
Study Protocol Title:	A Randomized, Multicenter, Double-Blind, Superiority Study of Dotinurad (4 mg) and Febuxostat (40 mg) for the Treatment of Subjects With Gout
Investigational Product Name:	FYU-981/dotinurad

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with China Good Clinical Practice (C-GCP), including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date