Supplement 1

Study Protocol of the URIC CKD study

Study Protocol

Chronic kidney disease patients with hyperuricemia and hypertension. Effects of uric acid-lowering agents (uric acid production inhibitors and excretion enhancers) on renal function decline

Urate lowering drugs Randomlzed parallel-group Comparison study in the Chronic Kidney Disease patients with hypertension and hyperuricemia (URIC CKD study)

Research Implementation Plan

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0. Synopsis

0.1 Objective

To assess the impact of uric acid production inhibitors (xanthine oxidase inhibitors) and uric acid excretion enhancers (uric acid transporter URAT 1 inhibitors) on renal function decline in patients with chronic kidney disease (CKD) complicated by hyperuricemia and hypertension.

0.2 Target population

Patients with CKD stage 3a-3b with hyperuricemia and hypertension

0.3 Study design

Multicenter, randomized, parallel two-arm study

0.4 Study schedule

Run in period (Visit1): 8 weeks of life guidance begins
Treatment phase 1 (Visit 2) Group A: Lifestyle guidance + URAT 1 inhibitor (benzbromarone)
Group B: Lifestyle guidance + xanthine oxidase inhibitor (febuxostat)
Start of administration
(Visit 3) 8 weeks after starting drug administration
Treatment phase 2: same drug as treatment phase 1 for another 44 weeks
Visit 4: 52 weeks after starting medication

0.5 Study drugs

Xanthine oxidase inhibitor: febuxostat (Feburic® Tablets)
URAT 1 inhibitor: benzbromarone (Urinorm® tablet)

0.6 Endpoints

(1) Primary endpoints
Percentage and absolute change in eGFR at 52 weeks (1 year) from the value immediately before the start of drug administration
(2) Secondary endpoints
1) Percentage and absolute change in eGFR at Week 8 after initiation of treatment
2) Percentage and absolute change in office blood pressure at 8 & 52 weeks after initiation of treatment
3) Difference in percent Percentage and absolute change in eGFR at 8 & 52 weeks before and after initiation of treatment
4) Percentage and absolute change in serum uric acid level and rate of attainment of serum uric acid level below 6.0 mg/dL at weeks 8 & 52 after initiation of treatment
5) Percentage and absolute change in urinary albumin/creatinine ratio at weeks 8&52 after initiation of treatment (%)
6) Percentage and absolute change in urine pH at 8&52 weeks after initiation of treatment
7) Percentage and absolute change in XO activity at 8&52 weeks post-dose initiation
8) Percentage and absolute change in hs-CRP at 8&52 weeks after initiation of treatment
9) Percentage and absolute change in urinary 8-OHdG (8-hydroxy-2'-deoxyguanosine) at weeks 8 & 52 after initiation of treatment
10) Percentage and absolute change in urinary angiotensinogen at weeks 88&52 after initiation of treatment
11) Proteinuria for the primary endpoint, stratified analysis by renal function

1. Background

The prevalence of hyperuricemia in Japanese adult males is thought to be as high as 30% after the age of 30 and is still rising.[1] 1) Hyperuricemia is linked to the occurrence and progression of chronic kidney disease (CKD). Epidemiological studies have demonstrated that serum uric acid level is a risk factor for the development of CKD and that there is a strong correlation between serum uric acid level and the deterioration of renal function.[2-4] Particularly, the association between uric acid and CKD has been demonstrated to be common in hypertensive patients.[5] Because the risk of end-stage renal failure and cardiovascular disease rises with the progression of CKD, [6, 7] intervention for hyperuricemia in hypertensive patients with CKD may not only prevent renal function decline but also improve patient prognosis.
Studies using an animal hyperuricemia model have shed light on the mechanism underlying CKD progression by hyperuricemia. Uric acid-induced-renal microvascular lesions are thought to play a key role in the development of hypertension and renal damage. [8,9] Inflammation, oxidative stress,

and the renal renin-angiotensin system have been also proposed as potential contributors to the mechanism of microvascular lesions.[10] According to our research, hyperuricemia affects renal microvascular lesions in CKD patients without regard to other comorbid conditions like hypertension or diabetes mellitus.[11] Renal arteriolar lesions may aid in the progression of renal damage through glomerular hypertension and ischemia, two common mechanisms of renal damage. They may also aid in the development of cardiovascular disease by raising blood pressure.

Several prospective interventional trials have reported that xanthine oxidase (XO) inhibitors, which reduce uric acid production, prevent GFR decline in CKD patients. Urate transporter 1 (URAT1) is expressed on the cell membrane of vascular cells and has all been suggested to be linked to intracellular oxidative stress, inflammation, and uric acid-induced enhancement. [12, 13] Therefore, URAT 1 inhibitors are anticipated to improve renal microvascular lesions and slow the development of CKD. It is currently unknown whether the reduction of uric acid itself, inhibition of XO activity, or inhibition of URAT1 causes the inhibition of CKD progression.

Febuxostat, an XO inhibitor with a novel mechanism of action, is a uric acid-lowering drug that was authorized for the treatment of gout and hyperuricemia in Japan in January 2011. Clinical trials have demonstrated that febuxostat has excellent serum uric acid-lowering abilities and it is effective and safe in patients with mild to moderate renal dysfunction,[14] and the approval of febuxostat broadens treatment options for hyperuricemia. Benzbromarone received approval in August 1978 to treat hyperuricemia brought on by gout and hypertension. It reduces hyperuricemia by specifically preventing uric acid reabsorption in the tubules (URAT 1 inhibition) and encouraging uric acid excretion into the urine.

In this parallel-group study, we will evaluate the effects of febuxostat and benzbromarone on eGFR and the effects of blood pressure, urinary albumin excretion, XO-active oxidative stress, inflammatory markers, and renal RA system markers of hypertensive patients with chronic kidney disease and hyperuricemia

2. Objective

To assess how febuxostat and benzbromarone affect renal function in CKD patients with hyperuricemia and hypertension

3. Target population

3.1 Target Patients

Patients with CKD stage 3a-3b with hyperuricemia and hypertension

3.2 Inclusion criteria

Patients who meet the following criteria shall be included (1) through (7) at the time of eligibility determination.

① Serum uric acid level greater than 7.0 mg/dL
② Hypertension (untreated patients with an office blood pressure of 140/90 mmHg or higher or on antihypertensive medication) who have not changed their antihypertensive medication for 8 weeks before the eligibility determination
③ CKD stage 3a-3b
(4) Age 20 years or older at the time of obtaining consent
(5) Outpatients
6) Patients with no history of gout
(7) Patients who have given their written informed consent to participate in the study.

[Rationale]

① The definition of hyperuricemia was set following the definition of hyperuricemia in the Guidelines for the Treatment of Hyperuricemia and Gout (2nd edition)16).
② An association between hyperuricemia and the progression of CKD has been prevalent in patients with hypertension. (Ref)
③ Urate lowering therapy is a favor for slowing the decline in eGFR in CKD patients.
④ The subjects were adults. The upper limit of age was not set to examine the significance in actual clinical practice.
⑤ The study was limited to outpatients with relatively stable medical conditions.

(6) This was set in consideration of the need for drug treatment based on the treatment

guidelines for hyperuricemia and gout [1].
(7) Participation in the study was set because it was based on the free will of the patients themselves.

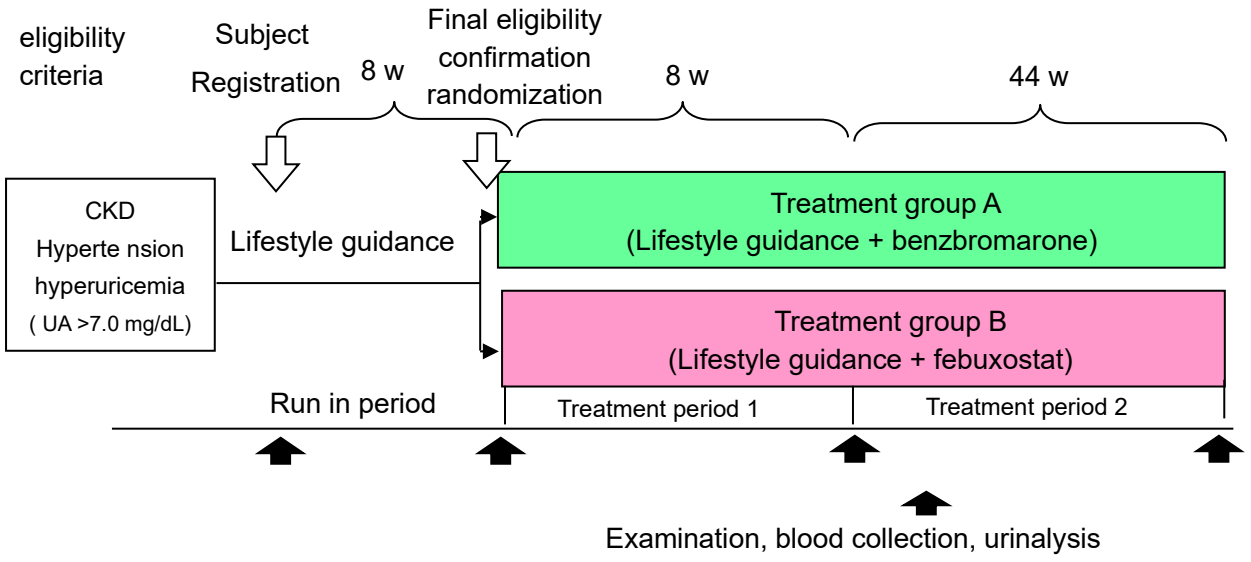
3.3 Exclusion Criteria
If any of the following items (1) through (13) are violated at the time of eligibility determination, the company shall be excluded from the scope.

① History of hypersensitivity to the drugs used
② AST or ALT is more than twice the institutional standard value
③ Severe renal dysfunction (eGFR less than 30 mL/min./1.73m2 or more than 60 mL/min./1.73m2, dialysis patients)
④ Under medication with thiazide diuretics, loop diuretics
⑤ Under medication with urate lowering drugs in the 2 weeks before an eligibility determination
⑥ Patients who developed coronary artery disease within 3 months before an eligibility determination
⑦ History of malignancies (unless the malignancy has been untreated for at least 5 years since the time of eligibility determination and is judged not to have recurred)
⑧ Patients receiving any of the following drugs
Mercaptopurine hydrate, azathioprine, pyrazinamide, ethambutol
⑨ Under medication with warfarin
⑩ Patients who are lactating, pregnant, or may be pregnant
⑪ Patients who have participated in other clinical studies (including clinical trials) within 6 months before an eligibility determination
⑫ Urinary tract stones
⑬ Other patients whom the physician in charge judges to be unsuitable as subjects.
⑭ Patients with serum uric acid levels below 7.0 mg/dl in the post-visit 2 lifestyle guidance phase will not be randomized to the treatment phase. (Final eligibility check)
⑮ Patients with a history of acute myocardial infarction, acute coronary syndrome, coronary artery stenosis intervention (catheterization and coronary artery bypass surgery), ventricular tachycardia, multisource ventricular arrhythmia, or acute heart failure within 3 months before the time of eligibility determination (newly added based on the results of the CARES study)

[Rationale]
Febuxostat is contraindicated in patients receiving the drugs listed in ⑧. It may potentiate the effect of warfarin

4. Research plan

4.1 Design of the study
Multicenter, randomized, parallel two-arm study



4.2 Expected number of participants and implementation period

Expected number of participants: 100 (50 in each of treatment groups A and B)

Research period: After approval by the Ethical Review Committee - February 28, 2021

Research registration period: After approval by the Ethical Review Committee - November 30, 2018

The basis for setting the number of expected participants.

We predicted that a sample size of 100 participants the study would provide 90% power to detect differences in the primary outcome (change in eGFR) of 15 mL/min/1.73m2 per year between the randomized groups based on the findings of previous studies,[14, 15] assuming a standard deviation of 20 mL/min/1.73m^2, a drop-out rate of 20%, a type I error rate of 5%, and the use of a two-sided significance test.

4.3 Case Registration and Assignment Methods

After verifying the eligibility of the candidate patients and obtaining their written consent to participate in the study, the physician in charge creates a case registration form and submits it to the research secretariat for case registration. The research secretariat will verify the case registration form's information. Additionally, the research secretariat will fill out the reply column on the case registration form with the eligibility determination results and, if applicable, the allocation results (treatment group A or treatment group B), and then return it to the physician in charge.

The research office members in charge of allocation will generate random numbers to distribute assignments according to an allocation table they have created. The research secretariat's person in charge of allocation will be the only one with knowledge of and strict control over the allocation table. The allocation factors will be determined using the data at the time of eligibility confirmation, which will include the following four items: age 70 years or older, gender, percentage of patients with CKD stage 3b, and presence of urinary albumin of 300 mg/gCr or higher.

4.4 Details of the research treatment

The attending physician will begin the research treatment depending on the results of the allocation.

(1) Run in period

During the Run in phase (8 weeks), lifestyle advice (diet, alcohol consumption restriction, exercise recommendations, etc.) will be given regarding the Guidelines for the Treatment of Hyperuricemia and Gout (2nd edition)[16).]

(2) Treatment period 1

Following final eligibility determination, febuxostat 10 mg/day or benzbromarone 25 mg/day will be administered in treatment phase 1 after confirming tolerability, along with lifestyle recommendations. The daily dosage of febuxostat will be increased to 20 mg/day beginning in week 5. Treatment should last for 8 weeks.

(3) Treatment period 2

A serum uric acid level of less than 6 mg/dl should be attained by adjusting the medication used in treatment phase 1. The recommended course of treatment is 44 weeks (1 year from the start of the drug).

If gouty arthritis appears during the observation period, the dosage of benzbromarone, and febuxostat should be continued without modification in principle. For benzbromarone, use Urinorm® tablets, and Feburic® tablets for febuxostat.

4.5 Combination therapy

In principle, the type, dosage, or administration of concomitant medications should not be changed during Treatment Periods 1 and 2. However, this does not apply to cases where intensification of treatment is required because of deteriorating renal or blood pressure function, or where changes in treatment are necessary to address other complications. Patients

receiving benzbromarone should be advised to drink water, and urine alkalinization should be considered if the patient's urine is acidic.

4.6 Notification to other departments and hospitals

The treating physician will determine if the patient is visiting another department or hospital. If the subject is visiting another department or hospital, the head doctor and the subject's attending doctor at the other department or hospital will be notified of the subject's participation in this study.

4.7 Completion, discontinuation, and suspension of study

(1) Criteria for completion of study

Subjects will be discontinued from the study if any of the following occur

a) Ineligibility as a subject

(1) If it is discovered after the study has begun that the subject was ineligible for inclusion and exclusion requirements, etc.

(2) If it is discovered after the research has begun, the patient's circumstances or other factors make it impossible to continue conducting the required observations (examinations).

(3) If it comes to light that you are pregnant or think you might be.

If the uric acid level falls to less than 3 mg/dl following the start of administration

b) The subject's offer (withdrawal of consent)

If a subject case requests to discontinue participation in the study after it has begun

c) Transfer to another hospital

If the study's subject case is moved to a different hospital after it begins

d) clinical development

(1) If the subject passes away following the start of the research

(ii) If, following the start of the research, the subject becomes unable to follow the protocol due to cardiovascular complications (onset or worsening of heart failure, acute myocardial infarction, cerebrovascular accident, new onset of peripheral arterial disease, or the introduction of renal replacement therapy).

e) Discontinuation due to the onset of adverse events

If adverse events, etc. make it impossible to follow the implementation plan

f) Other

When the in-charge doctor determines that the research should be stopped.

(2) Procedure for discontinuing the research

If the subject is determined to fall under the discontinuation criteria, the physician in charge will explain this and stop the research.

If a safety issue, such as the occurrence of an adverse event, requires the study to be terminated, the responsible physician will take prompt appropriate measures and, in theory, will continue to monitor the patient until recovery or until it is decided that additional investigation is not required.

If it is discovered after the study has begun that the subject is unable to travel to the hospital due to circumstances, etc., the subject's health will be confirmed by telephone, etc., along with the reason for the absence and safety of the subject will be confirmed.

The physician in charge of cases where the research has been stopped should detail the date of discontinuation, the reason for discontinuation, the processing, observations up to Visit 3 (week 8), and Visit 4 (week 52), even after discontinuation for potential cases, test results that can be gathered, and subsequent progress in the case report form.

5. survey items and schedule

5.1 Schedule

The responsible doctor will conduct observations and examinations according to the following schedule. The results should be described in the case report.

	Run in period (Visit 1) *3	Treatment phase 1 (short-term effects) Visit2*4 Visit3		Treatment phase 2 (long-term effects) Visit4
		Just before the start	8 weeks later	52 weeks later
Subject background	●			
Height*1, weight, abdominal circumference*1	●	●	●	●
Blood pressure, pulse rate	●	●	●	●
AST, ALT, TC*5, LDL*5, HDL*5, TG*5, serum uric acid, HbA1c, GLU, serum creatinine*2 Na, K, Cl	●*3	●	●	●
Plasma XO Activity		●	●	●
Inflammatory Markers		●	●	●
Oxidative Stress Markers		●	●	●
Urinary angiotensinogen		●	●	●
Urinary L-FABP		●	●	●
urinalysis	●	●	●	●
Medication status of research drugs			●	●
Concomitant medications		●	●	●
adverse event		→	→	→

*1 Height and abdominal circumference can be measured once during the study participation period.

*2 Calculate eGFR using the estimation formula of the Japanese Society of Nephrology.

*3 Test results within 4 weeks before the time of eligibility determination shall be made available.

Visit 3 test results will be available within 2 weeks before and after the test.

Visit 4 test results will be available within 4 weeks before and after the test.

After final eligibility confirmation, serum uric acid levels below 7.0 mg/dl will not be entered into the treatment phase.

If there is no value measured by a medical institution, the value is automatically calculated by a formula.

TC-HDL-C-(TG/5)=LDL-C

5.2 Survey items

(1) Background of subjects

The following items shall be investigated when determining eligibility.

Age, gender, CKD stage, blood pressure, renal function, pre-existing conditions, and complications

(2) Height, weight, and abdominal circumference

Weight will be measured when determining eligibility, before the start of each treatment period, and after each treatment period. Height will be measured once during the study participation period. Concurrent pharmaceuticals (antihypertensive agents, diuretics, antidiabetic agents, lipid agents, basic renal failure agents)

(3) Blood pressure and pulse rate

At the time of eligibility determination, before the start, and after each treatment period, blood

pressure, and pulse rate will be checked after resting in a sitting position for 5 minutes.

(4) Blood test, renal function

The following items will be measured when determining eligibility determination, Run period, and moments before, 8W after, and 52W after initiation of therapeutic agents. When determining eligibility, test results from 4 weeks before the time of eligibility determination will be available for the determination.

AST, ALT, TC, LDL, HDL, TG, serum creatinine, Na, K, Cl, serum uric acid, HbA1c, GLU

Calculate the eGFR using the following formula13).

eGFR (mL/min/1.73m^2)=194 x Cr^-1.094 x Age^-0.287 (x 0.739 for women)

(5) Plasma XO activity

Measurements will be taken shortly before the start of therapeutic agents, 8W after the start, and 52W after the start. For measurement, samples are frozen at -80°C, and batch measurement is conducted when the number of samples is available.

(6) Inflammatory markers, oxidative stress markers, renal RA system markers, and tubulointerstitial damage markers

Measurements will be taken shortly before therapeutic agents begin, 8W after the start, and 52W after the start. Samples will be frozen at −80°C for measurement, and batch measurement will be conducted when the number of samples is adequate. Among the following items, inflammatory markers, oxidative stress markers, and urinary L-FABP will be assessed by SRL Co.

Inflammatory markers: high sensitivity CRP
Oxidative stress markers:
Urinary 8-OHdG (8-hydroxy-2'-deoxyguanosine)
Urinary angiotensinogen
Urinary L-FABP

(7) Urinalysis (microalbuminuria and urine pH, urine Na, urine UA)

(Early morning) Use urine as needed. (Early morning) Use urine as needed.

(8) Inspection for safety confirmation

In addition to the aforementioned, AST, ALT, serum creatinine, Na, K, Cl, serum uric acid, and urinalysis will be conducted on each outpatient clinic day from 8W to 52W to track the side effects of hepatic and renal disorders.

(9) Compliance with research treatment

After each treatment period, the subjects will be questioned about the study drugs' medication status in the following four stages.

(1) I almost took it (more than 90%)
(2) Sometimes forgot to take the medication (more than 70% to less than 90%)
(iii) More than half of them took it (more than 50% to less than 70%)
④ Less than half of the patients took the drug (less than 50%)

(10) Concomitant medications

No drug modifications will be made during the Run in phase and Treatment phase 1 if possible. The types and daily doses of antihypertensive drugs, diuretics, antidiabetic drugs, lipid drugs, and basic renal failure drugs until the conclusion of the study will be evaluated.

(11) Adverse events

Assess adverse events during study participation

(12) Data collection

Data collection will be performed by a clinical research coordinator affiliated with the implementing medical institution or the researcher's institution.

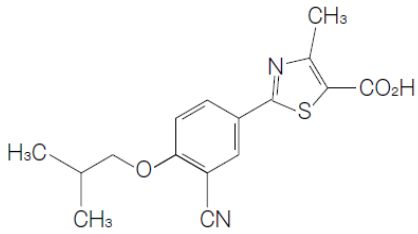
6. Overview of the research agent

6.1 Research Drug Information

Generic name: Febuxostat (febuxostat)

Chemical name: 2[-3-cyano-4(-2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid

Chemical structural formula :



Molecular formula : C16H16N2O3S

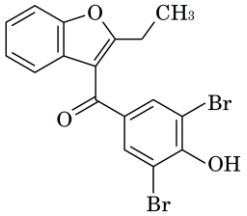
Trade Name: Feburic® Tablets 10 mg, Feburic® Tablets 20 mg, Feburic® Tablets 40 mg

For details, please refer to the attached document and interview form.

Generic name: benzbromarone

Scientific Name: 3 , 5-Dibromo-4-hydroxyphenyl 2-ethylbenzo[b]furan-3-yl ketone

Chemical structural formula:



Molecular formula: $C_{17}H_{12}Br_2O_3$

Trade Name: Benzbromarone® Tablets 25 mg, Benzbromarone® Tablets 50 mg

For specifics, please refer to the attached document and interview form.

6.2 Anticipated adverse reactions

The following side effects have been reported.

Excerpt from Febuxostat Appendix (Revised November 2013 (5th Edition))

(1) Serious adverse reactions: Hepatic dysfunction (frequency unknown), Hypersensitivity (frequency unknown)
(2) Other side effects

Type \ Frequency	Frequency unknownNote)	Less than 1-5	Less than 1
blood	thrombocytopenia anemia		decreased white blood cell count
endocrine			Increased TSH
nervous system	Headache, taste disorder		Tingling sensation in limbs, floating dizziness, somnolence
heart	pulsation		ECG abnormality
gastrointestinal			Diarrhea, abdominal discomfort, nausea, abdominal pain
Liver and Biliary System		Abnormal liver function test values [increased ALT (GPT), AST (GOT), γ-GTP, etc.].	
skin	urticaria		Rash, pruritus, erythema
musculoskeletal system		arthralgia	Limb pain, limb discomfort, increased CK (CPK)
Renal and urinary tract	decreased urine output		Increased beta-N-acetyl D-glucosaminidase, increased urinary beta2-microglobulin, increased blood creatinine, increased blood urea, frequent urination
Other	swelling		Fatigue, dry mouth, increased triglycerides in the blood, increased CRP

Note 1) Not observed in domestic clinical trials, but observed in foreign countries.

Excerpt from Benzbromarone® Tablets 25 mg, 50 mg (Revised May 2013 (11th Edition))

(1) Serious adverse reactions: Hepatic dysfunction (frequency unknown): Severe hepatic disorders such as fulminant hepatitis and jaundice may occur.
(2) Other side effects

Type \ Frequency	0.1% or more	Less than 0.1	Frequency unknown
HypersensitivityNote 1)	Itchiness, rash, urticaria	Facial redness, erythema	photosensitivity
LiverNote 2)	Increase in AST (GOT) and ALT (GPT) rise	Increase in Al-P	jaundice
digestive organs	Gastric discomfort, Gastrointestinal disorders, Diarrhea, Soft stools, Heartburn	Stomachache, abdominal pain, nausea, roughness in the mouth	
Other		Edema, cardiac discomfort, headache	

(Note 1) If any of these symptoms occur, the administration should be discontinued.
(Note 2) If such symptoms occur, the administration should be discontinued and appropriate measures should be taken.

7. Outcome variables

7.1 Outcomes
(1) Primary outcome
Percent and absolute change in eGFR between immediately before and 52 weeks (1 year) after initiation of treatment
(2) Subsidiary study outcomes
1) Percent and absolute change in eGFR at Week 8 after treatment initiation
2) Percent and absolute changes in office blood pressure at 8 & 52 weeks after treatment commencement
3) Difference in percent and absolute change in eGFR at 8 & 52 weeks before and after treatment commencement
4) Percent and absolute changes in serum uric acid level and rate of attainment of serum uric acid level below 6.0 mg/dL at weeks 8 & 52 after treatment commencement
5) P Percent and absolute change in urinary albumin/creatinine ratio at weeks 8&52 after treatment commencement
6) Percent and absolute change in urine pH at 8&52 weeks after treatment commencement (%)
7) Percent and absolute change in XO activity at 8&52 weeks post-dose commencement (%)
8) Percent and absolute change in hs-CRP at 8&52 weeks after treatment commencement (%)
9) Percent and absolute change in urinary 8-OHdG (8-hydroxy-2'-deoxyguanosine) at 8 & 52 weeks after treatment commencement (%)
10) Percent and absolute change in urinary angiotensinogen at 8&52 weeks after treatment commencement (%)
11) Percent and absolute change in urinary L-FABP at 8 & 52 weeks after treatment commencement (%)
12) Stratified analysis of primary and secondary outcomes by gender, proteinuria, and renal function

7.2 Statistical analysis
(1) Target population for analysis
Case handling will be assessed by the principal investigator. The largest Full Analysis Set will be presented as the patient population enrolled in the study, who have received at least one study treatment, and whose eGFR has been evaluated before and after the treatment initiation in treatment phase 1.

(2) Statistical analysis
ITT analysis will conduct the analyses. The subject background will be evaluated by

calculating frequency summaries or summary statistics for each allocation group and conducting Student's t-test and Pearson's chi-square test.

The primary endpoint will undergo an unpaired t-test (or non-parametric test in the case of non-normal distribution). For the secondary endpoints, the corresponding t-test (or non-parametric test for non-normal distribution) will be conducted. The rate of attainment of serum uric acid levels of 6.0 mg/dL or less will be compared using Pearson's chi-square test.

For adverse events, the frequency, and prevalence of occurrence will be calculated for each event.

The significance level of the test is 5% two-sided unless otherwise stated. For estimating intervals, 95% confidence intervals are used.

8. What to do in the event of an adverse event

If a negative event is noticed, the treating doctor should act right away to address it and document the progress in the patient's medical file. Adverse events should be reported in the case report form.

Adverse events that fall under the following categories should be reported to the medical institution's leader following the medical institution's regulations as serious adverse events.

(1) Deadly things
(2) A threat to life.
(3) Hospitalization for treatment or extension of hospitalization period
(4) Permanent or significant disability or malfunction
(5) Those with congenital anomalies.

9. Informed consent and provision of information to study participants

9.1 Explanation to the patient

Before patient registration, the attending physician should give the patient an explanation document authorized by the Ethical Review Committee and verbally explain the following details.

(1) Conducting the research
(2) Purpose of this study
(3) Duration of this study
Subjects of this study
5) Method of this study
6) About the flow of this research
⑦ Expected results of this study.
⑧ Advantages and disadvantages of the participants in this study
(ix) Cost sharing for this research.
(10) Health hazards during participation in this study
11) Freedom to participate in this research and withdrawal
⑫ Handling of personal information and research results
⑬ Conflict of interest
Monitoring and auditing
(xv) Contact information and contact details of the physician in charge

9.2 Obtaining Consent

The responsible physician will use the patient information document to verbally explain the research's contents to the candidate patient, give them time to consider it, and then ask them to participate in the study once they are sure they understand it completely. The consent form is signed by the patient if they consent to participate in the research. Verify that the consent form includes the name of the doctor who provided the explanation, the explanation's date, the patient's name who received the explanation and consented, and the date the consent was obtained. Make a copy of the consent form and give the patient. The original should be kept in the patient's medical file or another location specified by the hospital.

If during research participation information is learned that might influence a subject's decision to continue participating in the study or not, the information must be immediately explained to the subject, the subject's decision to continue participating in the study must be reaffirmed, and

this must be documented in the medical file. Every time the patient explanation document is updated, the subjects' written consent to continue participation in the study will be required.

9.3 Withdrawal of Consent

Even if a subject consents to participate in the study, he, or she has the right to leave at any time, for any reason. In such a situation, the physician in charge of the subject will give the best medical care attainable so that the subject will not suffer any kind of disadvantage.

10. Benefits and disadvantages of subjects

10.1 Profit

Due to the short duration of participation in the study, there will be no immediate benefits for the subjects, but the study may offer helpful information for the treatment and management of patients with hyperuricemia complicating chronic kidney disease.

10.2 Disadvantages

Although the study drugs (benzbromarone and febuxostat) are commonly used in daily practice as one of the uric acid production inhibitors, will be used in this study within the limits of the approved doses in this study, there is a possibility that the adverse reactions listed in "6.2 Expected adverse reactions" may occur. However, some of the negative effects listed in "6.2 Expected adverse reactions" might manifest. These adverse events may also occur in routine clinical practice, and participation in the study is not anticipated to increase the risk of adverse reactions.

The physician in charge will conduct the study with the highest priority on ensuring the safety of the subjects, and will promptly take appropriate measures to address any adverse events.

11. Ethical consideration

11.1 Compliance with ethical standards

All researchers in this research will conduct this research following the Declaration of Helsinki (revised in 2013) and the Ethical Guidelines for Medical Research Involving Human Subjects (Ministry of Education, Culture, Sports, Science, and Technology and Ministry of Health, Labor and Welfare, enforced in 2015).

The principal investigator should obtain and store the consent explanatory documents and opt-out documents approved by the assigned research organization.

11.2 Revision of the Implementation Plan

If the principal investigator determines that the protocol must be revised, he, or she will do so. If it is determined necessary to revise the consent explanatory document due to a change in the content of the protocol, the principal investigator will promptly revise it and obtain renewed consent from patients who gave consent before the revision, whether they wish to continue participating in the research or not. If it is deemed necessary to revise the consent document due to changes in the content, the document will be revised promptly, and the patients who gave consent before the revision will be asked whether they wish to continue participating in the research or not.

11.3 Reporting to the Head of the Research Organization

The principal investigator must submit a written report to the director of the research institution every year following the start of the study, except times when the research protocol is revised or when a serious adverse event occurs, when this study is discontinued or when there is a serious deviation from the protocol.

11.4 Protection of Personal Information

Handle patients' data (samples, medical information, etc.) with care and ensure the protection of their privacy.

In data reporting, a code for patient identification (personal identification code) is used and

no personal information is required (anonymization). Each anonymized information in the Department of Cardiovascular, Nephrology, and Neurology, Graduate School of Medicine, University of the Ryukyus will be managed by the information manager (Ryo Zamami) on a dedicated computer that is not linked to the Internet. Additionally, each facility will keep a list of the correspondence between personal identification codes and personal information. The list of correspondence between personal identification codes and personal information will not be presented to the secretariat or Hisatomi Arima, the person in charge of analysis. Verify the method of obtaining IC at each facility, as well as if appropriate procedures are being followed by those providing samples and information. The principal investigator and the person in charge at the collaborating institution must fully control the patient study-related samples and not take them out of the hospital. Furthermore, the samples will be stored until five years after the completion of the research or three years after the publication of the results, whichever is later.

11.5 Health Damage Compensation

Since benzbromarone and febuxostat are already covered by insurance, no compensation will be given for health problems, and health problems will be treated using normal health insurance.

What to do in the event of a health hazard

Emergency relief for patients does not depend on the presence or absence of negligence, the percentage of negligence, or the causal link with the target drug.

The priority will be given to implementation.

Despite the proper use of the target drugs specified in this study following the instructions of the physician in charge

For health damage brought on by side effects that occur, the use of the drug is within the scope of the indication, so the drug is subject to adverse drug reactions.

The Harm Reduction Program applies to it.

11.6 Secondary Use of Information

The potential for secondary use of the data collected for this study for other studies, etc., should be discussed in the explanatory document, and the subject's written consent should be obtained. Before using the data from this study is to be used for unrelated purposes, the study plan must receive the Ethical Review Committee’s approval. Subjects who previously gave their consent for this protocol (Version 5.0) will be re-consented for secondary use.

12. Handling of samples and information

The E RED Cap of the Center for Clinical Research Education and Management at the University of the Ryukyus will serve as the study's EDC system. Essential documents related to this study (e.g., copy of application form, notification letter from the hospital director, consent form, case report form, patient identification code, and other documents or records necessary to ensure the accuracy of the data) will be kept in the Department of Cardiovascular, Nephrology, and Neurology, Graduate School of Medicine, University of the Ryukyus, will retain key study records for 5 years following the study’ conclusion. Data from patients who withdraw their consent will be destroyed immediately. Blood samples collected and stored for this study will be discarded after the necessary marker measurements are completed.

13. Cost burden for subjects

The cost of measuring the inflammatory markers and oxidative stress needed for this study will be covered by research funds. All additional medications, observations, and tests necessary for this study will be covered by insurance. Therefore, there will be no additional burden on subjects due to participation in the study.

Subjects who partook in the study will be rewarded for their cooperation with rice vouchers worth 3,000 yen at three points: just before the start of the study, at 8 weeks, and 52 weeks.

14. Quality control and reliability assurance

14.1 Monitoring

Monitoring will be performed to ensure that the study is being conducted safely and based on the protocol and that data are being collected appropriately.

Monitoring officer: Shinichiro Ueda, Director, Center for Clinical Research Education and Management

The monitoring items shall be as follows, and the implementation of on-site monitoring shall be deemed necessary.

1) Process for obtaining consent and storage of consent forms
2) Eligibility
3) Observed item data
4) Adverse events (especially serious adverse events and their reporting status)
5) Protocol treatment status
6) Other

14.2 Auditing

An audit will be conducted to ensure the reliability of this research.

Audit Manager: Katsunori Nakamura, Deputy Director, Clinical Research Support Center

The audit will focus on the following items

1) Status of compliance with ethical guidelines and research protocol
2) Process for obtaining consent and storage of consent forms
3) Ethical Review Status
4) Occurrence and review status of serious adverse events
5) Accuracy of collected data items
6) Other

14.3 Research Support

The University of the Ryukyus will dispatch research assistants when requested by other institutions.

15. Research funding sources and conflicts of interest

The funds for this study will be contributed by Teijin Pharma Limited based on a joint research agreement with the Third Department of Internal Medicine. Teijin Pharma Limited will not partake in any way in the management of this study, including planning, execution, analysis, and publication. Participants in this study are required to abide by the conflict of interest management guidelines and shall not break them.

16. Disclosure of information on research and publication of research results

16.1 Clinical Research Registration

This study has been registered in the University Hospital Medical Information Network Clinical Trials Registration System ((identification number: R000029056)) before the start of the study and the information has been made public.

16.2 Research presentation

After the completion of the research, the principal investigator will promptly summarize the results and publish them by presenting them at a conference or submitting a paper.

17. Research organization

17.1 Principal Investigator

Summarize the operation of this study.
Dr. Kohagura K, Dialysis Unit, University of the Ryukyus Hospital

17.2 Research Assignments

Prof. Arima H, Department of Preventive medicine, and Public Health, Fukuoka University, (Statistical analyst)

Dr. Sakima A, Health Management Center, University of the Ryukyus Center

Dr. Ishida A, Department of Cardiovascular Medicine, Nephrology and Neurology, Graduate School of Medicine, University of the Ryukyu

Dr. Masayuki Yamazato, Department of Cardiovascular Medicine, Nephrology and Neurology, Graduate School of Medicine, University of the Ryukyu

Dr. Zamami R, Department of Cardiovascular Medicine, Nephrology and Neurology, Graduate School of Medicine, University of the Ryukyu

Dr. Nakamura T, Department of Cardiovascular Medicine, Nephrology and Neurology, Graduate School of Medicine, University of the Ryukyu

Dr. Nakachi M, Department of Medical Education Planning, University of the Ryukyus (Inclusion of subjects)

17.3 Collaborative Research Facilities

Shurijyokmachi Clinic, Nanbu Hospital, Nakagami Hospital, Kaiho Hospital,

17.4 Research secretariat

Dr. Kentaro Kohagura Dialysis Unit, University of the Ryukyus Hospital
TEL：098-895-3331 FAX：098-895-1501 E-mail： kohagura@med.u-ryukyu.ac.jp

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11. Kohagura K, Kochi M, Miyagi T, Kinjyo T, Maehara Y, Nagahama K, et al.: An association between uric acid levels and renal arteriolopathy in chronic kidney disease: a biopsy-based study. H*ypertens Res,* 36: **4**3-49, 2013 10.1038/hr.2012.135
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Supplement 2

Statistical Analysis Plan (SAP) for URIC CKD study

Statistical Analysis Plan (SAP) for Urate lowering drugs Randomized parallel-group Comparison study in the Chronic Kidney Disease patients with hypertension and hyperuricemia (URIC-CKD study)

Version: 2.0

Date: 2020/05/07 (Translated on 7 Aug 2021)

Principal Investigator:

Associate Professor Kentaro Kohagura

Department of Blood Purification Therapy, University of Ryukyus Medical School

Author of SAP:

Professor Hisatomi Arima

Department of Preventive Medicine and Public Health, Fukuoka University

Contents

1. Objective

The objective of this Statistical Analysis Plan (SAP) is to define detailed method for data management and statistical analysis for “Urate lowering drugs Randomized parallel-group Comparison study in the Chronic Kidney Disease patients with hypertension and hyperuricemia (URIC-CKD study)”.

2. Study design

Summary of research is shown below.

2-1. Study objective

To evaluate the effect of uric acid production inhibitors (xanthine oxidase inhibitors) and uric acid excretion enhancers (uric acid transporter URAT 1 inhibitors) on renal function decline in patients with chronic kidney disease (CKD) complicated by hyperuricemia and hypertension.

2-2. Target population

2-2-1. Inclusion criteria

Patients must meet all of the following criteria (1) through (7) at the time of eligibility determination.

(1) Patients with a serum uric acid level greater than 7.0 mg/dL
(2) Patients with hypertension (untreated patients with an office blood pressure of 140/90 mmHg or higher or on antihypertensive medication) who have not changed their antihypertensive medication for 8 weeks prior to the eligibility determination
(3) Patients with CKD stage 3a-3b
(4) Age 20 years or older at the time of obtaining consent
(5) Outpatients
(6) Patients with no history of gout
(7) Patients who have given their written consent to participate in the study.

2-2-2. Exclusion criteria

If any of the following items (1) through (13) are violated at the time of eligibility determination, the company shall be excluded from the scope.

(1) Patients with a history of hypersensitivity to the drugs used
(2) Patients whose AST or ALT is more than twice the institutional standard value
(3) Patients with severe renal dysfunction (eGFR less than 30 mL/min./1.73m2 or more than 60 mL/min./1.73m2, dialysis patients)
(4) Patients taking thiazide diuretics, loop diuretics
(5) Patients who have received uric acid lowering drugs in the 2 weeks prior to eligibility determination

(6) Patients who developed coronary artery disease within 3 months prior to eligibility determination
(7) Patients with concomitant or prior malignancies (unless the malignancy has been untreated for at least 5 years since the time of eligibility determination and is judged not to have recurred)
(8) Patients receiving any of the following drugs: mercaptopurine hydrate, azathioprine, pyrazinamide, ethambutol
(9) Patients taking warfarin
(10) Patients who are lactating, pregnant, or may be pregnant
(11) Patients who have participated in other clinical studies (including clinical trials) within 6 months prior to eligibility determination
(12) Patients with urinary tract stones
(13) Other patients whom the physician in charge judges to be unsuitable as subjects.
(14) Patients with serum uric acid levels below 7.0 mg/dl in the post-visit 2 lifestyle guidance phase will not be randomized to the treatment phase. (Final eligibility check)
(15) Patients with a history of acute myocardial infarction, acute coronary syndrome, intervention for coronary artery stenosis (catheterization and coronary artery bypass surgery), ventricular tachycardia, multisource ventricular arrhythmia, or acute heart failure within 3 months prior to the time of eligibility determination (newly added based on the results of the CARES study)

2-3. Study design

A multi-center, randomized, parallel-group comparison trial

2-4. Random allocation

Participants will be randomly allocated to:
Treatment group A (lifestyle guidance + benzbromarone) or
Treatment group B (lifestyle guidance + febuxostat)

2-5. Research treatment

URAT 1 inhibitor: benzbromarone (Urinorm® tablet)
Xanthine oxidase inhibitor: febuxostat (Feburic® Tablets)

2-5-1. Run in period

During the Run in phase (8 weeks), lifestyle guidance (diet, restriction of alcohol consumption, exercise recommendations, etc.) will be given with reference to the Guidelines for the Treatment of Hyperuricemia and Gout (2nd edition).

2-5-1. Treatment period 1

After final eligibility determination, febuxostat 10 mg/day or benzbromarone 25 mg/day will be administered in treatment phase 1 after confirming tolerability in addition to lifestyle guidance. The dose of febuxostat will be increased to 20 mg/day from week 5. The duration of treatment should be 8 weeks.

2-5-2. Treatment period 2

The medication used in treatment phase 1 should be adjusted to achieve a serum uric acid level of less than 6 mg/dl. The treatment period should be 44 weeks (1 year from the start of the drug).

2-6. Endpoint

2-6-1. Primary endpoint for efficacy

Change in eGFR from immediately before initiation of randomized treatment (visit2) to 52 weeks after initiation of treatment (visit 4):

(eGFR at visit 4 – eGFR at visit2) / eGFR at visit 2 [unit: % / 52 weeks] and
eGFR at visit 4 – eGFR at visit 2 [unit: ml / min / 1.73m^2 / 52 weeks]

2-6-2. Secondary endpoint for efficacy

(1) Change in eGFR from immediately before initiation of randomized treatment (visit2) to 8 weeks after initiation of treatment (visit 3) [unit: % / 52 weeks and ml / min / 1.73m^2 / 8 weeks]
(2) Change in office blood pressure from immediately before initiation of randomized treatment (visit2) to 8 & 52 weeks after initiation of treatment (visits 3 & 4) [unit: % / 8 weeks, % / 52 weeks, mmHg / 8 weeks and mmHg / 52 weeks]
(3) Difference in change in eGFR from immediately before initiation of randomized treatment (visit2) to 8 weeks after initiation of treatment (visit 3) (per 4 weeks) and change in eGFR from 8 weeks to 52 weeks after initiation of treatment (visit 4) (per 4 weeks) [unit: % / 4 weeks and ml /min / 1.73m^2 / 4 weeks]
Difference in change in eGFR from immediately before initiation of randomized treatment (visit2) to 52 weeks after initiation of treatment (visit 4) (per 4 weeks) and change in eGFR from initiation of run-in period (visit 1) to initiation of randomized treatment (visit 2) (per 4 weeks) [unit: % / 4 weeks and ml /min / 1.73m^2 / 4 weeks]
Difference in change in eGFR from 8 weeks (visit 3) to 52 weeks after initiation of treatment (visit 4) (per 4 weeks) and change in eGFR from initiation of run-in period (visit 1) to initiation of randomized treatment (visit 2) (per 4 weeks) [unit: % / 4 weeks and ml /min / 1.73m2 / 4 weeks]
(4) Change in serum uric acid level from immediately before initiation of randomized treatment (visit2) to 8 & 52 weeks after initiation of treatment (visits 3 & 4) [unit: % / 8 weeks, % / 52

weeks, mg / dl / 8 weeks and mg / dl / 52 weeks]
Rate of attainment of serum uric acid level <6.0 mg/dl at 8 & 52 weeks after initiation of treatment (visits 3 & 4) [unit: %]

(5) Change in urinary albumin / creatinine ratio from immediately before initiation of randomized treatment (visit2) to 8 & 52 weeks after initiation of treatment (visits 3 & 4) [unit: % / 8 weeks, % / 52 weeks, mg / gCr / 8 weeks and mg / gCr / 52 weeks]

(6) Change in urine pH from immediately before initiation of randomized treatment (visit2) to 8 & 52 weeks after initiation of treatment (visits 3 & 4) [unit: % / 8 weeks, % / 52 weeks, absolute change / 8 weeks and absolute change / 52 weeks]

(7) Change in XO activity from immediately before initiation of randomized treatment (visit2) to 8 & 52 weeks after initiation of treatment (visits 3 & 4) [unit: % / 8 weeks, % / 52 weeks, pmol IXP / min / mL / 8 weeks and pmol IXP / min / mL / 52 weeks]

(8) Change in hs-CRP from immediately before initiation of randomized treatment (visit2) to 8 & 52 weeks after initiation of treatment (visits 3 & 4) [unit: % / 8 weeks, % / 52 weeks, mg / dL / 8 weeks and mg / dL / 52 weeks]

(9) Change in urinary 8-OHdG（8-hydroxy-2'-deoxyguanosine ） from immediately before initiation of randomized treatment (visit2) to 8 & 52 weeks after initiation of treatment (visits 3 & 4) [unit: % / 8 weeks, % / 52 weeks, ng / mL / 8 weeks and ng / mL / 52 weeks]

(10) Change in urinary angiotensinogen from immediately before initiation of randomized treatment (visit2) to 8 & 52 weeks after initiation of treatment (visits 3 & 4) [unit: % / 8 weeks, % / 52 weeks, μg / gCr / 8 weeks and μg / gCr / 52 weeks]

(11) Change in urinary L-FABP from immediately before initiation of randomized treatment (visit2) to 8 & 52 weeks after initiation of treatment (visits 3 & 4) [unit: % / 8 weeks, % / 52 weeks, μg / gCr / 8 weeks and μg / gCr / 52 weeks]

2-7. Sample size estimation

Expected number of participants: 100 (50 in each of treatment groups A and B)

［Rationale for sample size estimation］

The main objective of this study was to exploratively investigate the effect of febuxostat administration and benzbromarone on renal function in patients with hyperuricemia complicated by chronic kidney disease. Based on the results of previous studies, we expected the difference between the two treatments to be eGFR/52W 15 ml/min/1.73m^2.[1, 2] Then, we calculated α0.05, power 0.8, δ15, σ20, and dropout rate as 20%.

2-8. Follow-up duration

Participants will be followed up for 52 weeks (treatment period 1 for 8 weeks and treatmentperiod 2 for 44 weeks).

2-9. Research period

Research period: from approval by the Ethical Review Committee to February 28, 2021
Registration period：from approval by the Ethical Review Committee to November 30, 2018

3. Analysis population

Full analysis set (FAS): In accordance with the intention to treat (ITT) principle, all patients except for those without information after randomization will be included in the analysis.

Per protocol set (PPS): Sensitivity analysis excluding participants with protocol violation might be conducted.

Safety analysis set (SAS): All patients except for those without any information after randomization who received any randomized treatment will be included in safety analysis.

4. Data management

4.1. Handling of follow-up survey results

Survey will be conducted at initiation of run-in period (visit 1), immediately before initiation of randomized treatment (visit 2), and 8 & 52 weeks after initiation of treatment (visits 3 & 4). Visit 3 survey results within 2 weeks of the planned visit will be used for statistical analysis and visit 4 survey results within 4 weeks of the planned visit will be used for statistical analysis. When participants are complicated with concomitant disease which can affect eGFR, survey results after onset of the disease will be deled as missing values.

4.2. Missing values

In principle, missing values will not be imputed.

4.3. Outlier

Outliers may be deled as missing values based on consensus in medicine.

4.4. Transformation of continuous variables

A continuous variable, which does not follow a normal distribution, may be log-transformed.

5. Statistical analysis

5.1. Basic rule

The level of statistical significance will be 0.05 (two-sided). A continuous variable will be summarized as mean, SD, median, interquartile range, number of participants with missing values. A categorical variable will be summarized as number of cases, percentage, number of participants with missing values. Denominator of percentage will be number of participants with

available data.

5.2. Participant flow

Number of registered participants, randomized participants, analysis population, treatment discontinuation and drop-out will be summarized in **Figure (Participant flow）**.

Participants who did not receive randomized treatment, those who were excluded after registration, those who discontinued treatment or dropped out will be summarized by reason. Drop-out rate will be estimated as number of participants with discontinuation and drop-out / number of FAS. These results will be included in **Figure (Participant flow）**.

5.3. Baseline characteristics

Baseline characteristics, test results and concomitant treatment will be summarized by randomized groups in **Table（characteristics, test results and concomitant medications）.**

5.4. Primary analysis

Change in eGFR from immediately before initiation of randomized treatment (visit2) to 52 weeks after initiation of treatment (visit 4):

(eGFR at visit 4 – eGFR at visit2) / eGFR at visit 2 [unit: % / 52 weeks] and

eGFR at visit 4 – eGFR at visit 2 [unit: ml / min / 1.73m^2 / 52 weeks]

will be estimated and compared between randomized groups using unpaired t-test or analysis of variance (ANOVA). Mean differences in eGFR change between randomized groups, 95% confidence intervals and p values will be estimated. If there is significant imbalance in important factors in baseline characteristics, analysis of covariance (ANCOVA) will be used as sensitivity analysis. If missing values in the primary outcome are observed among ≥5% of participants, multiple imputation will be conducted as sensitivity analysis. These results will be summarized in **Table (Primary analysis)**.

5.5. Secondary analysis

5.5.1. Secondary outcomes

Same analysis approach as the primary outcome will be applied to secondary outcomes. With regard to rate of attainment of serum uric acid level <6.0 mg/dl at 8 & 52 weeks after initiation of treatment, odds ratios, 95% confidence intervals and p values will be estimated using Fisher's exact test, chi-squared test and/or logistic regression models. If there is significant imbalance in important factors in baseline characteristics, multivariable logistic regression models will be used as sensitivity analysis. These results will be summarized in **Table (Seconary analysis)**.

5.5.2. Repeated measure analysis of primary outcome

Change in eGFR from immediately before initiation of randomized treatment (visit2) to 8 & 52 weeks after initiation of treatment (visits 3 & 4) will be used as repeated measure and overall mean differences in eGFR change between randomized groups, 95% confidence intervals and p values will be estimated using Generalized Estimating Equations (GEE). Overall mean change in eGFR and 95% confidence interval in each randomized group will also be estimated. If there is significant imbalance in important factors in baseline characteristics, GEE including such factors as covariates will be used as sensitivity analysis. These results will be summarized in **Table (Repeated measure analysis of primary outcome)**.

5.6. Medications

Study treatment and concomitant medications at 8 & 52 weeks will be summarized in **Table (Medications).**

5.7. Safety analysis

Serious adverse events during study treatment will be summarized by randomized groups in **Table (Safety outcomes)**. Serious adverse events reported by physician will be used for the analysis. The difference in frequency of serious adverse events will be compared between randomized groups using chi-squared test and results will be summarized in **Table (Safety outcomes)**.

5.8. Subgroup analysis

Subgroup analysis stratified by gender, proteinuria, renal function, obesity (BMI ≥ 25kg/m^2), median of XO activity, median of hs-CRP, diabetes (HbA1c ≥6.5%, diabetic pattern in OGTT or use of glucose lowering treatment) will conducted for primary and secondary outcomes and summarized in**Table (Subgroup analysis)**. These subgroups were defined before data lock.

5.9. Observational analysis

Factors associated with change in eGFR, urinary albumin / creatinine ratio, office blood pressure and XO activity from immediately before initiation of randomized treatment (visit2) to 8 & 52 weeks after initiation of treatment (visits 3 & 4) will be investigated. Factors associated with baseline XO activity will also be investigated.

6. Statistical software

SAS Version 9.4（SAS Institute Inc.）and STATA 15 (StataCorp LLC) will be used for statistical analysis.

7. List of figures and tables

Figure. Participant flow

Table. Baseline characteristics, test result and concomitant medications

Table. Primary analysis

Table. Secondary analysis

Table. Repeated measure analysis of primary outcome

Table. Medications

Table. Safety outcomes

Table. Subgroup analysis

8. References

1. Sircar D, Chatterjee S, Waikhom R, Golay V, Raychaudhury A, Chatterjee S, Pandey R: Efficacy of febuxostat for slowing the GFR decline in patients with CKD and asymptomatic hyperuricemia: A 6-month, double-blind, randomized, placebo-controlled trial. Am J Kidney Dis, 66: 945-950, 2015 10.1053/j.ajkd.2015.05.017

2. Kohagura K, Tana T, Higa A, Yamazato M, Ishida A, Nagahama K, et al.: Effects of xanthine oxidase inhibitors on renal function and blood pressure in hypertensive patients with hyperuricemia. Hypertens Res,39: 593-597, 2016 10.1038/hr.2016.37

Supplementary Table 1 . Primary outcome with adjustment and per-protocol analysis

Percent change/absolute change from week 0 to week 52 of drug initiation	estimated value (95% CI) Benzbromarone	Febuxostat	difference	*P* value
Primary outcome (adjusted for diabetes and drinking status)				
eGFR, mL/min/1.73m^2 per 52 weeks	-1.70 (-3.64, 1.23)	0.27 (-1.66, 2.23)	1.98 (-2.32, 10.12)	0.216
eGFR, % per 52 weeks	-3.35 (-7.74, 1.03)	0.55 (-3.84, 1.93)	3.90 (-0.77, 4.72)	0.216
Primary outcome (per-protocol)				
eGFR, mL/min/1.73m^2 per 52 weeks	-2.36 (-4.03, -0.69)	-0.23 (-1.99, 1.54)	2.13 (-0.13, 4.56)	0.084
eGFR, % per 52 weeks	-4.95 (-8.68, -1.23)	-0.74 (-4.68, 3.21)	4.21 (-1.21, 9.64)	0.126

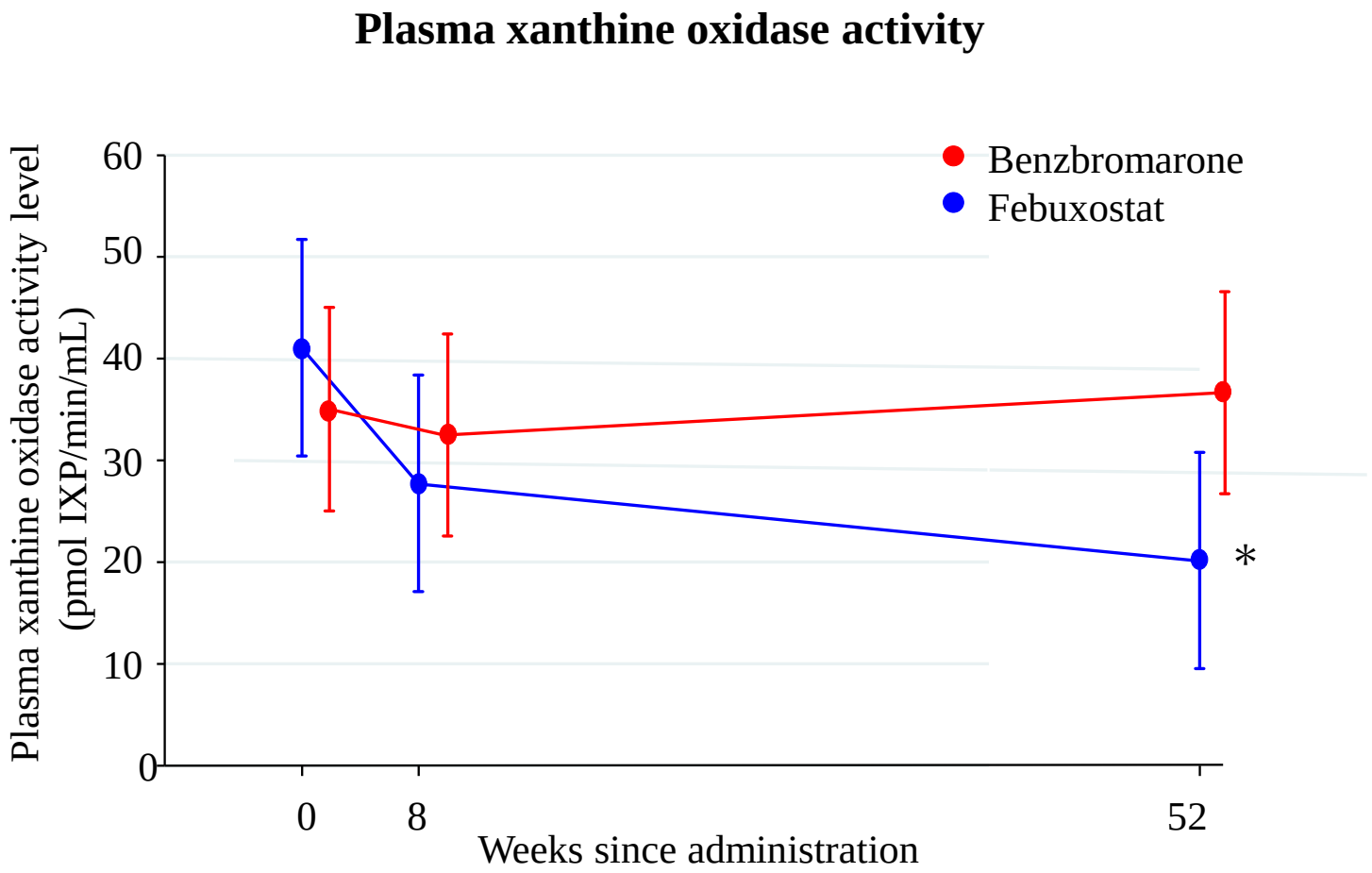
Abbreviations: eGFR, estimated glomerular filtration rate

Supplementary Table 2. Secondary outcome regarding slope of eGFR

	estimated value (95% CI)			
Difference of slope of eGFR	Benzbromarone	Febuxostat	difference	*P* value
Week -8–0 → Week 0–52				
ΔeGFR, mL/min/1.73m^2 per 4 weeks	-0.46 (-1.30, 0.38)	0.10 (-0.80, 1.00)	0.56 (-0.67, 1.79)	0.368
eGFR, % per 4 weeks	-1.47 (-3.41, 0.47)	-0.37 (-2.45, 1.71)	1.10 (-1.75, 3.94)	0.445
Week -8–0 → Week 0–8				
ΔeGFR, mL/min/1.73m^2 per 4 weeks	0.00 (-1.22, 1.23)	0.29 (-1.02, 1.60)	0.29 (-1.50, 2.09)	0.748
eGFR, % per 4 weeks	-0.41 (-3.26, 2.45)	0.11 (-2.95, 3.16)	0.52 (-3.66, 4.70)	0.807
Week -8–0 → Week 8–52				
ΔeGFR, mL/min/1.73m^2 per 4 weeks	-0.55 (-1.34, 0.25)	0.05 (-0.80, 0.90)	0.60 (-0.56, 1.76)	0.308
eGFR, % per 4 weeks	-1.66 (-3.51, 0.19)	-0.44 (-2.43, 1.54)	1.22 (-1.50, 3.94)	0.375

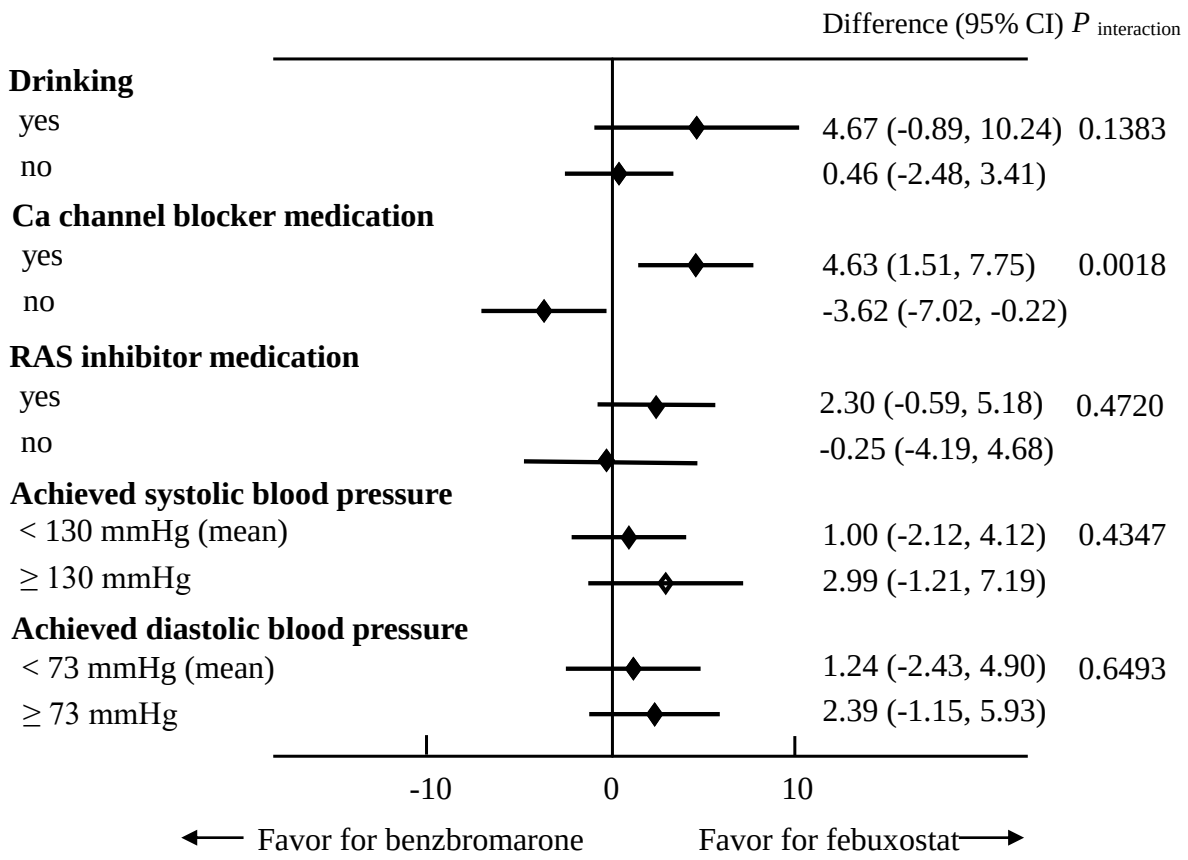
Abbreviations: eGFR, estimated glomerular filtration rate

Supplementary Figure 1



* P < 0.05 versus baseline

Supplementary Figure 2



Supplementary Figure 3