DOTINURAD

PROTOCOL UR1-DOT-103

A PHASE 1B OPEN LABEL EVALUATION OF PK AND PD OF DOTINURAD AND THE DRUG-DRUG INTERACTION OF DOTINURAD AND ALLOPURINOL IN U.S. PATIENTS WITH GOUT AND HYPERURICEMIA

Sponsor:

Urica Therapeutics, Inc.

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Version 1.1 (FINAL)

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for dotinurad. I confirm that I have read this protocol. I understand it, and I will work according to the protocol and moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the principles of ICH guidelines for GCP and according to applicable local regulatory requirements. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1 Emergency Contact Information (Study UR1-DOT-103)

Role in Study	Name	Contact Information
Clinical Study Leader	Mike Ryan	Urica Therapeutics, Inc.
Medical Monitor	Jeffrey D. Lazar MD, PhD	Lotus Clinical Research 203 912-3932

1. SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsor/Company: Urica Therapeutics, Inc.</td></tr>
<tr><td colspan="2">Name of Investigational Product: Dotinurad</td></tr>
<tr><td colspan="2">Name of Active Ingredient: Dotinurad</td></tr>
<tr><td colspan="2">Title of Study: A Phase 1B Open Label Evaluation of the PK and PD of dotinurad and Drug-Drug Interaction of dotinurad and Allopurinol in U.S. Patients with Gout and Hyperuricemia</td></tr>
<tr><td colspan="2">Study center: Multicenter in the United States</td></tr>
<tr><td>Studied period:
Estimated date first subject enrolls: Q2 2023
Estimated date last subject completes: Q3 2023
Estimated date primary analysis: Q4 2023</td><td>Phase of development: 1B</td></tr>
<tr><td colspan="2">Objectives:
This study has two objectives:
1. To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of 7 days of treatment with two doses of dotinurad monotherapy, and
2. To evaluate the effect of dotinurad, as monotherapy and in combination with allopurinol, versus allopurinol monotherapy, on the PK of each, and to assess the additive PD effects on serum uric acid and urinary urate excretion in U.S. patients with gout and hyperuricemia.
The safety/tolerability of each treatment (monotherapy dotinurad, combination of dotinurad and allopurinol, and monotherapy allopurinol) will also be assessed.
To achieve this objective, this study will evaluate the pharmacokinetics (PK), pharmacodynamics (PD), and safety/tolerability of 7 days of treatment with dotinurad monotherapy, followed by 7 days of treatment with concomitant allopurinol and dotinurad, and then followed by 7 days of treatment with allopurinol monotherapy. Two dose regimens of dotinurad (2 and 4 mg, once-daily) will be assessed in combination with allopurinol 300 mg once-daily.
Specific objectives include assessment of coadministration dotinurad and allopurinol dosing over 7 days vs monotherapy dosing of each alone on:
• Pharmacokinetics (serum and urine);
• Uricosuric response (serum uric acid and urinary uric acid excretion);
• Safety and tolerability.</td></tr>
<tr><td colspan="2">Study Design:
This is a Phase 1B, open-label, open label, 3-period, multi-center multidose, PK/PD and drug-drug interaction (DDI) study. A total of N=20 eligible patients with gout and hyperuricemia will, following at least 14 days of washout of urate lowering therapy (ULT) and open-label treatment with Colchicine 0.6 mg QD, be)assigned to one of 2 cohorts (N=10 patients each to cotinurad 2 mg or to dotinurad 4 mg) and then treated with open-label study medication (given once-daily in the morning)</td></tr>
</table>

for 7 days in each of 3 treatment periods (Table 1). Patients will continue with Colchicine 0.6 mg QD until the end of follow-up period.

Two doses of dotinurad (monotherapy and in combination with allopurinol) are being studied (dotinurad 2 mg and dotinurad 4 mg), with allopurinol 300 mg, with both medications given QD in the morning. Patients, Investigators and the Sponsor will not be blinded, and thus will be aware of the treatments given to each patient during each treatment period. Patients will be admitted to the CRU on the evening of Day -2 OR the morning of Day -1 to obtain baseline measurements for blood samples, a 24-hour urine collections (which will end shortly prior to the first dose of dotinurad on Day 1), and other scheduled assessments. Patients will remain in the CRU through the morning of Day 8, receiving daily morning doses of dotinurad on Days 1 through 7. Following the Day 7 dose, patients will undergo 24 hour serum and urine sampling, ending on the morning of Day 8 (prior to dosing with concomitant dotinurad and allopurinol). Patients will be discharged on the morning of Day 8, after having completed their PK and PD sampling procedures and after having received their first dose of treatment with concomitant dotinurad and allopurinol.

On Days 9, 10, 12, and 13, sites will conduct a daily telehealth visit (phone-call or video-call) to confirm that they have taken dotinurad with allopurinol and to provide a health check and reminder of hydration. On Day 11, patients will have a full safety laboratory assessment (in-clinic), which will include a serum creatinine test for renal function.

Patients will be re-admitted to the CRU on the evening of Day 13 OR early on the morning of Day 14. Following the Day 14 dose of concomitant dotinurad and allopurinol, patients will undergo 24 hour serial blood samples, 24-hour urine collections, and other scheduled assessments, ending on the morning of Day 15 (prior to dosing with allopurinol only). Patients will be discharged on the morning of Day 15 having completed their PK and PD sampling procedures and after having received their first dose of treatment with allopurinol monotherapy.

On Days 16 to 20, patients will conduct a daily telehealth visit to confirm that they have taken allopurinol and to provide a health check and reminder of hydration.

Patients will be re-admitted to the CRU on the evening of Day 20 OR early on the morning of Day 21. Following the Day 21 dose of allopurinol, patients will undergo 24 hour serial blood samples, 24-hour urine collections, and other scheduled assessments, ending on the morning of Day 22.

Patients will be encouraged to be well hydrated by consuming 2L of liquids a day during each day of the study. Patients will have a telephone follow-up on Day 28.

Table 1: Study Design, Cohort Sequence of Treatment, and Treatment Periods (StudyUR1-DOT-103)

Screening (Days -28 to -15)	**Washout of Prior Meds (Days -14 to -1)**	**Period 1 (Days 1 to 7) In-clinic**	**Period 2 (Days 8 to 14)**	**Period 3 (Days 15 to 21)**	**Follow-Up (Days 22 to 28)**
	Colchicine 0.6 mg/day (can start any time at least 2 weeks prior to Day 1)				
Cohort 1	N=10 patients	dotinurad 2 mg/day	dotinurad 2 mg/day Allopurinol 300 mg/day	Allopurinol 300 mg/day	Follow-up period and scheduled telehealth call
Cohort 2	N=10 patients	dotinurad 4 mg/day	dotinurad 4 mg/day	Allopurinol 300 mg/day	Follow-up period and scheduled telehealth call

			Allopurinol 300 mg/day		

The study has 5 general study periods:

1. Screening and washout
   - Screening (Days -28 to -15). Initial eligibility determination. Please note that if a patient is on urate lowering therapy (ULT) prior to screening, all other eligibility should be met during Screening period other than sUA. In these patients, the required fasting sUA level is =>8 mg/dl between Day -7 and Day -1. If a patient is not on ULT prior to Screening, the required fasting sUA level is =>8 mg/dl during Screening.
   - Washout of Uric-Acid-Lowering Drugs and Open-Label Treatment with colchicine 0.6 mg QD (Days -14 to -1 but can start as early as Day -28 if eligibility is confirmed at that time). Consent must be obtained prior to the start of washout of ULT and treatment with colchicine.
     - Treatments for the patients underlying gout/hyperuricemia (eg, allopurinol) will be reviewed at screening. All patients will be required to discontinue urate lowering medications at least 14 days prior to check in at the CRU on Day -1. Patients will also initiate treatment with open-label colchicine 0.6 mg QD (once daily each morning) at least 2 weeks (14 days) prior to check-in to the CRU. Colchicine is used for prophylaxis against gout flares during those 2 weeks while patients may be washing out of any other treatments for their underlying gout condition and will be continued throughout the study and follow-up period.
     - Importantly, initiation of colchicine treatment should be done at the same time the patient is washed out (ie, discontinues) any urate lowering medications, and can be up to 28 days prior to check-in at the CRU on Day -1.
2. Treatment period 1 (dotinurad monotherapy)
   - Admission to CRU (evening Day -2 or early morning Day -1) and in-Clinic stay through the morning of Day 8.
   - Day -1 to morning of Day 1: Confirmation of eligibility and final baseline/pre-treatment assessments. Collection of 24-hour urine collection.
   - Days 1 through 7 In-Clinic Dosing with dotinurad monotherapy
     - Open-label treatment each morning through Day 7 with dotinurad (2 mg for Cohort 1, 4 mg for Cohort 2)
     - Days 1, 4, and 7, following morning dose of dotinurad, 24-hour serum and urine collection for PK and PD
     - Days 2, 3, 5 and 6, trough samples (pre-dose) will be collected for serum PK and serum PD
3. Treatment period 2 (combination of dotinurad and allopurinol)

- Discharge morning of Day 8 after pre-dose PK/PD sample collection and first dose with concomitant dotinurad (2 mg for Cohort 1, 4 mg for Cohort 2) and allopurinol 300 mg QD for all patients.
- Period 2 (Days 9, 10, 11, 12, 13) Out-Patient Dosing with Concomitant dotinurad/Allopurinol, Day 11 safety laboratory samples collected (in-clinic).
  - Telehealth visits (phone call or video-call) will be scheduled daily for confirmation of doses, a health check and a reminder for hydration.
  - On Day 11, patients will have a full safety laboratory assessment (in-clinic), which will include a serum creatinine test for renal function.
  - Check-in to CRU (evening of Day 13) OR early on the morning of Day 14
  - Day 14 morning dose with concomitant dotinurad (2 mg for Cohort 1 and 4 mg for Cohort 2) and allopurinol 300 mg QD for all patients and then 24-hour serum and urine collection for PK and PD through morning of Day 15

4. Treatment period 3 (allopurinol monotherapy)
   - Period 3 (Days 15 through 21) Out-Patient Dosing with Monotherapy Allopurinol
     - Discharge morning of Day 15 after pre-dose PK/PD sample collection and first dose with monotherapy allopurinol 300 mg. Open-label treatment continues each morning through Day 20. Telehealth visits will be scheduled daily for confirmation of doses, a health check, and a reminder for hydration.
     - Check-in to CRU (evening of Day 20) OR early the morning of Day 21
     - Day 21 morning dose with monotherapy allopurinol and then 24-hour serum and urine collection for PK and PD through morning of Day 22
5. End of Study follow-up period
   - End of Study Safety Follow-Up (Days 22 through 28)
     - Discharge morning of Day 22 after final PK/PD sample collection and safety assessments. Note that dosing with allopurinol is discontinued, with no dose given on Day 22.
     - Note that colchicine treatment will continue through the end of this safety follow-up period (Day 28). Patients are permitted to recommence their prior uric-acid-lowering medications during this follow-up period, under their physicians care and instruction.
     - Final safety follow-up phone call on Day 28.

Number of subjects (planned):

Total number planned: A total of N=20 patients will be in the study (N=10 to Cohort 1, dotinurad 2 mg, and N=10 to Cohort 2, dotinurad 4 mg). Patients discontinuing prematurely may be replaced at the discretion of the PI and Sponsor.

Diagnosis and main criteria for eligibility:

Inclusion Criteria:

1. In the opinion of the investigator, the patient is capable of understanding and complying with protocol requirements.
2. Patients with a diagnosis of gout based on American College of Rheumatology criteria (1997). Patients must fulfill at least 3 of the following, with one of those 3 being (i) hyperuricemia.
    a. More than one attack of acute arthritis
    b. Maximum inflammation developed within 1 day
    c. Monoarthritis attack
    d. Redness observed over joints
    e. First metatarsophalangeal joint painful or swollen
    f. Unilateral first metatarsophalangeal joint attack
    g. Unilateral tarsal joint attack
    h. Tophus (proven or suspected)
    i. Hyperuricemia.
    j. Asymmetric swelling within a joint on x-ray
    k. Subcortical cysts without erosions on x-ray
    l. Monosodium urate monohydrate microcrystals on joint fluid during attack
    m. Joint fluid culture negative for organisms during attack
3. The patient signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures including requesting that a patient fast for any laboratory evaluations.
4. Negative COVID-19 test by either PCR or rapid antigen test at screening and check-in prior to first period, and agrees to be compliant with all COVID-19 measures mandated by the CRU prior to screening/entry into the trial.
5. Male or female between 18 and 75 years of age (inclusive). To be eligible, females can be either of NCBP (confirmed by surgical history, medical history of twelve consecutive months of amenorrhea, or FSH levels) or females of childbearing potential must be on a reliable method of birth control and also have a negative urine human chorionic gonadotropin (hCG) pregnancy test results on the Study Day -1.
6. Screening serum uric acid level of ≥7 mg/dl.
    a. If a patient is not on uric acid-lowering therapies (ULT) prior to screening, the required fasting sUA level is at least one ≥7 mg/dl during Screening
    b. If a patient is on ULT prior to screening, the required fasting sUA level is at least one =>7 mg/dl between Day -7 and Day -1
7. Screening liver enzymes (LFTs) <1.5x ULN. Total bilirubin ≤1x ULN. For patients with documented Gilbert Syndrome, total bilirubin ≤3 x ULN with direct bilirubin <1x ULN.
8. Screening renal function eGFR ≥ 60 mL/min/1.73m2.
9. Pre-dose hemoglobin should be within the normal range.
10. Body mass index (BMI) ≥ 18.5 and ≤ 40.0 (kg/m2) and a body weight of no less than 50 kg.
11. Medically healthy with no clinically significant screening results including but not limited to:
    a. Laboratory profiles other than sUA
    b. Urinalysis

c. Vital signs
d. Electrocardiograms (ECGs)
e. Physical examination

12. No use of tobacco or nicotine containing products (including smoking cessation products), for a minimum of 3 months prior to dosing.

Exclusion Criteria:

1. The subject has current or historical evidence of any clinically significant disease or condition that might complicate the subject's participation, or, in the opinion of the Investigator, may place the subject at an unacceptable risk as a participant in this trial, may interfere with the interpretation of safety and/or tolerability data obtained in the trial, or may interfere with the absorption, distribution, metabolism, or excretion of the study drug.
2. Patients with unstable angina, New York Heart Association Class III or IV heart failure, myocardial infarction, stroke, or deep venous thrombosis within 1 year prior to Day 1.
3. QT interval corrected for heart rate according to Fridericia's formula >470 msec in females and >450 msec in males during Screening, confirmed by a repeat assessment.
4. History of or presence of kidney stones.
5. History of or presence of malignancy in the last 5 years other than treated cutaneous basal or squamous cell carcinoma.
6. Urological disorder not well controlled.
7. Peptic ulcer disease requiring active treatment.
8. Cannot safely discontinue uric acid-lowering medication 14 days prior to study start to 9 days after the last dose of study medication was administered.
9. Surgery within the past 90 days prior to dosing as determined by the Principal Investigator to be clinically relevant.
10. Use of agents that could confound serum uric acid analysis (eg, long-term use of salicylates >100 mg or use of losartan).
11. Patients with an acute gout flare during the screening period that had not resolved 1 week prior to the first dose of study.
12. Hypersensitivity or intolerance to allopurinol, dotinurad or colchicine.
13. Positive for HLA-B*58:01 allele
14. History or presence of alcoholism or chronic drug abuse within the past 2 years.
15. Psychiatric disorder or social situation that prevents compliance with the protocol.
16. Female patients who are pregnant or lactating.
17. Positive results for the urine drug /alcohol breath test/cotinine at check-in.
18. Positive results at screening for Human Immunodeficiency Virus (HIV), Hepatitis B Surface Antigen (HBsAg), Hepatitis C antibodies (HCV).

19. Patient's semi-recumbent blood pressure is less than 90/40 mmHg or greater than 155/90 mmHg during Screening and Day -1.
20. Stable dose of medications for long-term conditions such as diabetes, high cholesterol, hypertension, asthma, etc. are allowed (provided that the patient has been on a stable dose for at least 30 days prior to Screening and is not expected to require dose adjustment during the study through 7 days post study).
21. Patient reports receiving a strong or moderate inhibitor of CYP3A4 or a P-gp inhibitor within 1 month prior to study drug dosing, due to potential interactions with colchicine.
22. Patient has taken azathioprine, Imuran, or other medications that may interact with allopurinol within 1 month prior to study drug dosing
23. Participation in another clinical trial within 30 days of last IP administration or 5 half-lives (whichever is longer) of administration of any study drug evaluated in that trial prior to screening for this trial. Previous participation in a dotinurad trial is also exclusionary.

Investigational product, dosage and mode of administration:

This is a Phase 1B study that assesses the PK and PD of dotinurad as well as the drug-drug interaction between dotinurad and allopurinol. The primary investigational product is dotinurad, while the coadministered product is allopurinol.

There are 2 dose levels of dotinurad to be studied:

- dotinurad 2 mg QD
- dotinurad 4 mg QD

Treatment will be given orally once-daily in the morning, according to the Schedule of Events and Period. Within each Period, dosing occurs for 7 days at approximately 30 minutes after finishing breakfast with 240 mL of water. It is strongly recommended that patients consume at least 2 Liters of liquids/day to ensure hydration.

Duration of treatment: This study includes treatment with both dotinurad and allopurinol. Patients will be treated for a total of 21 days, as follows:

- 7 days treatment with dotinurad (2 mg or 4 mg) QD monotherapy
- 7 days treatment with combination dotinurad (2 mg or 4 mg) QD and allopurinol 300 mg QD
- 7 days treatment with allopurinol 300 mg QD monotherapy

In addition, all patients will receive open-label colchicine 0.6 mg/day, starting during screening (Day -14 or earlier) as they washout of their prior uric-acid-lowering medications, and through at least Day 28 (end of follow-up period).

Reference therapy, dosage and mode of administration:

This is a PK, PD and drug-drug interaction study, in which the objectives are to assess the effects of coadministration on the PK and PD effects vs monotherapy administration of each. The primary investigational product is dotinurad, while the coadministered product is allopurinol.

There is one dose level of allopurinol to be studied:

- Allopurinol 300 mg QD

Treatment will be given orally once-daily in the morning, according to the Schedule of Events and Period. Within each Period, dosing occurs for 7 days at approximately 30 minutes after finishing breakfast with 240 mL of water. It is strongly recommended that patients consume at least 2 Liters of liquids/day to ensure hydration.

Criteria for evaluation:

This study has two objectives:

1. To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of 7 days of treatment with two doses of dotinurad monotherapy, and
2. To evaluate the effect of dotinurad, as monotherapy and in combination with allopurinol, versus allopurinol monotherapy, on the PK of each, and to assess the additive PD effects on serum uric acid and urinary urate excretion in U.S. patients with gout and hyperuricemia.

For the first objective, the following PK and PD assessments will be included.

- PK assessment will be performed of dotinurad (the parent) in both serum and urine. Plasma and urine sample collection will be performed throughout the course of the treatment period, with more intensive sampling on Days 1, 4, and 7. PK parameters will include (but are not limited to) AUC and Cmax (see the protocol body for the full list of parameters to be estimated). Attainment of steady state will be assessed for dotinurad using Helmert Contrasts on the trough concentrations from Days 2 through 8.
- PD assessments include serum uric acid lowering and urine urate excretion increase versus pretreatment. detailed assessments of these endpoints will be pretreatment and then Day 1, 4, and 7. PD endpoints will include area under the effect-time curve (AUEC) and maximum observed response (Emax), as well as fractional excretion of urate.

For the second objective, the following PK and PD assessments will be included.

- PK assessment of dotinurad, allopurinol, and oxypurinol after an oral dose on the 7th day of each treatment period will be determined for each treatment. Plasma PK parameters will include (but are not limited to) AUC and CMax (see the protocol body for the full list of parameters to be estimated). Urine PK parameters will include (but are not limited to) the amount excreted amount in urine (Ae) and the fractional excretion of urate (as a function of the total dose amount) (fe). The study will assess how the co-administration of dotinurad and allopurinol impacts the exposure level of the two drugs as compared to monotherapy.
- PD assessments of serum uric acid lowering and urine urate excretion observed on the combination therapy versus each monotherapy on the 7^{th} day of each treatment period will be determined. PD parameters will include uric acid area under the effect-time curve (AUEC) and maximum observed response (Emax). PD parameters, such as time-matched percentage change on the steady-state day (end of each treatment period) from baseline for sUA, urinary urate excretion (mg), and fractional excretion of urate will be calculated.

Use of two dose levels of dotinurad will also allow for assessment of dose-response.

Safety:

The safety/tolerability of each treatment (monotherapy dotinurad, combination of dotinurad and allopurinol, and monotherapy allopurinol) will also be assessed.

Safety endpoints will include treatment-emergent adverse events (TEAEs), clinical laboratory parameters, ECGs, vital signs, and physical examination.

Statistical methods:

The statistical methods to be used in the analysis are consistent with both the study design and the study objectives. A detailed statistical analysis plan (SAP) will be written; that SAP will describe, in detail, the methods to be used and will provide table, listing, and figure 'shells' that will demonstrate what those outputs will look like.

Note that the there are two objectives. The first objective is to assess the PK and PD of the two doses of dotinurad in U.S. patients with gout and hyperuricemia. The second objective is to identify whether there is a clinically meaningful PD or PK effect with coadministration of dotinurad and allopurinol, versus monotherapy administration of each. To that end, the analysis will be structured to allow for review of bioequivalence of the key PK parameters and assessment of differences in PD endpoints accordingly (eg, change and percent changes from baseline in uric acid, percent of patients with serum uric acid levels below various response definitions) under monotherapy vs coadministration. Graphics will be used extensively to present the outcomes across the PK and PD endpoints. As two doses of dotinurad are being studied, analysis of dose-response will also be performed.

Sample Size Considerations:

A sample size of n=10 patients per dotinurad dose level is sufficient to determine whether a PK or PD difference exists for those endpoints (both as a monotherapy and coadministered with allopurinol). This is based on observed coefficients of variation of PK parameters for prior dotinurad studies, as well as previous publications of similar studies with allopurinol (see Baumgartner 2018). Specifically, studies of dotinurad in Japanese patients have demonstrated low variability of PK and PD endpoints and have therefore required a small number of patients to demonstrate clear study outcomes.

Thus, a total of N=20 patients will therefore be sufficient to assess the PK and PD characteristics of two different dose levels of dotinurad in a drug-drug interaction study design.

Pharmacokinetics

PK parameters will be determined where possible from the plasma and urine concentrations of dotinurad, allopurinol, and oxypurinol using noncompartmental methods in validated software program.

Pharmacokinetic analysis will be carried out where possible using actual dose administered (mg) and actual postdose blood sampling times. If an actual time is missing, the sample concentration result will be treated as missing unless there is scientific justification to include the result using the nominal time. Assessment of the geometric ratio of key PK parameters (Cmax, AUC) will be performed to determine the differences (if any) between monotherapy vs combination therapy of each drug, with tests of bioequivalence (BE) performed accordingly vis assessment of the point estimates and 90% CIs vs (80%, 125%) confidence bounds for BE. Dose proportionality and dose response (eg, on exposure endpoints Cmax and AUC) between the two dotinurad dose levels will be performed.

Additional pharmacodynamic parameters will include time-matched percentage change from baseline (day –1) for serum uric acid concentrations and urinary urate excretion amount (mg). Dotinurad steady state will be assessed via Helmert Contrasts, using trough concentrations within Period 1 only.

Pharmacodynamics

Pharmacodynamic (PD) parameters will be determined where possible from the serum and urine concentrations of absolute uric acid and baseline-adjusted uric acid using noncompartmental methods in a validated software program. Comparison of the PD parameters between monotherapy and coadministration will be performed.

Response thresholds of serum uric acid levels will be determined using pre-dose concentrations on Days 7, 14, and 21, using <6 mg/dL, <5 mg/dL, and <4 mg/dL as prospectively defined response definitions. Dose proportionality and dose response (eg, on PD endpoints, vis-à-vis the number (%) of patients responding on serum uric acid by various response definitions) between the two dotinurad dose levels will be performed.

Safety

The safety analysis will be descriptive in nature. All safety data will be listed, and data will be tabulated where the data warrant. Adverse events will be coded using the MedDRA coding dictionary; subject incidence of each system organ class and unique term will be tabulated, as well as by severity and relationship to study treatment. AE incidence will also be tabulated according to relationship to study medication and severity. Serious AEs and AEs resulting in premature discontinuation will be tabulated.

Adverse events starting after the first dose of treatment will be considered treatment-emergent adverse events and will be reported as occurring during the treatment phase (period) they started in (and thus will be associated with the most recent treatment given). TEAEs occurring more than 7 days after discontinuation of study treatment will be classified as post-treatment emergent. Adverse events occurring after colchicine pre-treatment has begun but prior to the first dose of study medication will be considered pre-treatment events.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2 Abbreviations and Specialist Terms (Study UR1-DOT-103)

Abbreviation or special term	Explanation
°C	Degrees Celsius
°F	Degrees Fahrenheit
µM	Micromolar
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the concentration-time curve
$AUC_{0\text{-tlast}}$	Area under the concentration-time curve from time 0 to the last measurable concentration; calculated using linear trapezoid rule
$AUC_{0\text{-inf}}$	Area under the concentration-time curve from time 0 to infinity
$AUC_{0\text{-}24}$	Area under the plasma concentration vs. time curve from time 0 to 24 hours
BLQ	Below the Lower Limit of Quantitation
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
C_{12}	Plasma concentration at 12 hours after oral drug administration
C_{24}	Plasma concentration at 24 hours after oral drug administration
C_{max}	Maximum plasma concentration
C_{min}	Minimum plasma concentration
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CL/F	Oral clearance
CNS	Central nervous system
Conmed	Concomitant Medication
CRA	Clinical Research Associate
CRO	Clinical Research Organization
CRU	Clinical Research Unit
CV	Coefficient of variance
dL	Deciliter(s)
DMP	Data Management Plan
ECG	Electrocardiogram
eCRF	Electronic Case Report Form

Abbreviation or special term	Explanation
EDTA	Ethylenediaminetetraacetic Acid
FOB	Functional Observational Battery
FU	Follow-up
g	Gram
GCP	Good Clinical Practice
GGT	Gamma-glutamyl-transferase
HBsAg	Hepatitis B Surface Antigen
Hct	Hematocrit
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
Hgb	Hemoglobin
HPBL	Human Peripheral Blood Lymphocytes
hr(s)	Hour(s)
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
IUD	Intrauterine device
kg	Kilogram
L	Liter
LDL	Low Density Lipoprotein
mL	Milliliter
MedDRA	Medical Dictionary for Regulatory Activities
min(s)	Minute(s)
mg	Milligram
mL	Milliter
mm	Millimeter
msec	Millisecond
N/A	Not Applicable
ng	Nanogram
NOAEL	No Observed Adverse Effect Level
pH	Hydrogen Ion Concentration
PHI	Personal Health Information
PI	Protease inhibitor
PIS	Subject Information Sheet(s)

Abbreviation or special term	**Explanation**
PK	Pharmacokinetic
PR	Pulse Rate
QTc	The QTc interval is the corrected QT interval, adjusted for heart rate
RBC	Red Blood Cell
rpm	Revolutions Per Minute
RR	Respiratory Rate
RTV	Ritonavir
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source Document Verification
SpO_2	Blood oxygen saturation
$t_{1/2}$	Plasma elimination half-life
t_{lag}	Time to the first measurable plasma concentration
t_{max}	Time to reach peak plasma concentration
UDS	Urine Drug Screen
ULN	Upper limit of normal
V_{ss}	Apparent Volume of Distribution
WBC	White Blood Cell
WCT	WorldWide Clinical Trials
WHO	World Health Organization

4. INTRODUCTION

Dotinurad is a potent uricosuric agent developed and approved as a monotherapy in Japan for the treatment for hyperuricemia in patients with or without gout (under the trade name URECE®). The mechanism of action of dotinurad is well understood and depends on pharmacologic inhibition of URAT-1 (the primary transporter responsible for the normal renal tubular reabsorption of uric acid).

A previous Phase 1 study (FBIO-DOT-101), conducted in the U.S. in a 'western population', has characterized the safety/tolerability of a range of dose levels of dotinurad from 1 mg up to 8 mg. That study also described the pharmacokinetics (PK) and pharmacodynamics, ie, the uricosuric response to dotinurad in healthy patients with serum uric acid concentrations in the normal range. Data from that study demonstrated that the pharmacokinetics (PK) and pharmacodynamics (PD) in a US-derived Western population are similar to those observed in the dotinurad Japanese population database.

This current study's objective is to describe the pharmacokinetics (PK) and pharmacodynamics (PD) of three doses of dotinurad in a US-based sample of patients with gout and hyperuricemia. These data will be used to determine the dose level(s) to be carried into the Phase 3 clinical study program.

The objective of this new study is to provide data to enable decision-making as to the dose(s) to carry into the subsequent Phase 3 development program. Specifically, objectives include describing the pharmacokinetics of dotinurad (2 and 4 mg) once daily during 7 days of treatment, as well as describing the uricosuric response (serum uric acid and urinary uric acid excretion) over that time. The study will also provide data assessing the safety and tolerability of dotinurad in these patients, and in totality, provide support towards the bridging of the Japanese database for dotinurad to a U.S. population of gout patients.

4.1. Gout and Hyperuicemia

Gout is a condition characterized by the deposition of monosodium urate crystals in the joints or soft tissue. The four phases of gout include asymptomatic hyperuricemia, acute gouty arthritis, intercritical gout and chronic tophaceous gout. (Harris 1999).

The peak incidence occurs in patients 30 to 50 years old, and the condition is much more common in men than in women. Patients with asymptomatic hyperuricemia do not require treatment, but efforts should be made to lower their urate levels by encouraging them to make changes in diet or lifestyle. Acute gout (sometimes referred to as a flare) most commonly affects the first metatarsal joint of the foot, but other joints are also commonly involved. Acute gout is characterized by the sudden onset of pain, erythema, limited range of motion and swelling of the involved joint.

Asymptomatic hyperuricemia is the term for an abnormally high serum urate level, without gouty arthritis or nephrolithiasis. Hyperuricemia is defined as a serum urate concentration greater than 7 mg per dL (416 μmol per L), the approximate level at which urate is supersaturated in plasma.

The drugs available for the treatment of hyperuricemia in patients with gout are uricosuric agents (eg, probenecid, sulfinpyrazone), which increase the excretion of uric acid, and xanthine oxidase inhibitors (eg, allopurinol and febuxostat), which inhibit the oxidation of xanthine to uric acid.

4.2. Dotinurad

The clinical development program conducted by Fuji Yakuhin Co., Ltd and partners included treatment with dotinurad in more than 300 subjects in the Phase 1 program and over 750 patients in the Phase 2 and 3 program, in some patients for more than 1 year (Table 3). Doses from 0.5 mg up to 20 mg were studied in the Phase 1 program, while the Phase 2 and 3 program focused primarily on doses up to 4 mg.

Table 3: Japanese Development Program Exposure Database for Dotinurad

Population	PBO	Active Controls		mg Dose of Dotinurad							
		BENZ	FBX	0.5	1	2	4	5	10	20	All Doses
Healthy, Special Populations & Subjects with Hyperuricemia (Phase 1)	81	-	-	6	78	60	80	18	54	6	302
Subjects with Hyperuricemia (Phase 2/3)	59	99	101	40	62	259	61	-	-	-	423
Subjects with Hyperuricemia (Long-Term)	-	-	-	-	-	287	43	-	-	-	330
Total	**140**	**99**	**101**	**46**	**140**	**606**	**184**	**18**	**54**	**6**	

Abbreviations: BENZ = benzbromarone; FBX = febuxostat; PBO = placebo

During longer-term treatment with dotinurad, the most common adverse events were nasopharyngitis, gouty arthritis, arthralgia, CPK increased, and arthritis. Note that gout flares can occur with initiation of uric acid-lowering therapies (ULTs, including dotinurad). Prophylaxis against gout flares will be utilized in this clinical trial via treatment with colchicine for 2 weeks prior to initiation of treatment with dotinurad (or matching placebo), and will continue through the double-blind treatment period. Dotinurad increases renal excretion of uric acid, which may lead to increased risk of renal/urinary stones. Patients with a history of renal/urinary stones will be excluded from this Phase 1B study.

The potential of dotinurad to act as an interacting drug or an affected drug through inhibition or induction of metabolic enzymes, inhibition of transporters, or protein binding has been evaluated in previous studies; no drug-drug interactions have been identified. More detailed information is available in the IB.

4.2.1. Pharmacokinetic Profile

The pharmacokinetics of dotinurad have been characterized following single and multiple dosing in both healthy subjects and patient populations. The pharmacokinetics of dotinurad are well behaved and predictable, with exposure increased proportionally with dose up to doses well above the therapeutic dose in the Japanese population. There is minimal accumulation on repeat (once daily) dosing. No clinically significant food effect was observed.

Dotinurad pharmacokinetics appear to be unaffected by renal and hepatic impairment in clinical pharmacology studies designed to study these intrinsic factors. However, the uricosuric effect of dotinurad is attenuated by moderate renal impairment. No interactions between dotinurad and other drugs have been observed.

A small US-based Phase 1 study (FBIO-DOT-101) assessed the safety and tolerability of dotinurad doses (1, 2, 4, and 8 mg, vs placebo) in a 4-day treatment period crossover study with healthy subjects. The PK profile was similar to that observed in the Japanese database, with comparable PK parameters (Cmax, AUC) as well as comparable concentration-time profiles for similar dose levels.

4.2.2. Pharmacodynamic Profile

After daily oral administration of dotinurad in healthy adults, serum uric acid concentration decreases on Day 1, stabilizing from Day 3 onwards. Twenty-four hours after the last administered dose (Day 4), serum uric acid begins to return to pre-treatment values. A similar time course of effects on uric acid was observed in healthy US ('western') subjects.

Longer-term treatment (over 12 weeks) in a Japanese patient population with hyperuricemia demonstrated a dose-response (based on reduction of serum uric acid levels from an average at baseline of ~8.5 mg/dL) to ≤ 6.0 mg/dL at end of treatment (Table 4). Specifically, while the placebo arm demonstrated no response, the 2 mg and 4 mg dotinurad arms demonstrated 89.5% and 95.2% response, respectively.

Table 4: Number of Subjects Achieving Serum Uric Acid Levels < 6.0 mg/dL in a Japanese Population of Hyperuricemic Patients with or without Gout

Treatment group	Number of subjects	Number of subjects achieving serum uric acid level of ≤ 6.0 mg/dL (proportion of subjects %)		
		≤ 6.0 mg/dL	> 6.0 mg/dL	95% C.I. of proportion of subjects
Placebo group	19	0 (0.0)	19 (100.0)	0.0 to 17.6
FYU-981 1 mg group	20	15 (75.0)	5 (25.0)	50.9 to 91.3
FYU-981 2 mg group	19	17 (89.5)	2 (10.5)	66.9 to 98.7
FYU-981 4 mg group	21	20 (95.2)	1 (4.8)	76.2 to 99.9

A small US-based Phase 1 study (FBIO-DOT-101) assessed the safety and tolerability of dotinurad doses (1, 2, 4, and 8 mg, vs placebo) in a 4-day treatment period crossover study with healthy subjects. Serum uric acid concentrations began to decrease on Day 1, and appeared to stabilize from Day 3. Twenty-four hours after the last administered dose (Day 4), serum uric

acid began to return to pre treatment values. A similar general time course of effects on uric acid was observed in these healthy subjects at were observed in the Japanese database.

4.2.3. Clinical Safety

4.2.3.1. Japanese Development Program

Seventeen trials from the Japanese development program, including those in healthy patients with doses of up to 20 mg and studies in gout/hyperuricemia patients are described in more detail in the IB.

In an integrated analysis of those Japanese controlled double-blind studies with dotinurad, active comparators (febuxostat and benzbromarone), and placebo, the incidences of adverse events, drug-related adverse events, SAEs, drug-related SAEs, and discontinuations due to adverse events or drug-related adverse events did not differ greatly among the investigational product groups. One subject in the febuxostat group had a drug-related SAE; no subjects in any other treatment group had a drug-related SAE. There were no adverse events leading to death in any treatment group.

In the open-label long-term administration study, inspection of the adverse event and SAE rates in the two dose level groups (dotinurad 2 mg and 4 mg) were similar. Overall adverse event rates between the longer- and shorter-term studies did not reveal substantial differences in incidences across the doses of dotinurad studied.

In the controlled double-blind studies (including FYU-981-003), the most common adverse events with dotinurad treatment were nasopharyngitis (11.6%), gouty arthritis (5.5%), beta-Nacetyl-D-glucosaminidase (NAG) increased (3.6%), beta 2 microglobulin urine (BGM) increased (3.6%), and gamma-glutamyltransferase (γ-GTP) increased (2.1%). By comparison, the most common adverse events in the placebo group were nasopharyngitis (15.3%), increased BMG (6.8%), increased NAG (3.4%), limb discomfort (3.4%), increased blood creatine phosphokinase (CPK) (3.4%), increased alpha 1 microglobulin (AMG) (3.4%), and increased blood triglycerides (3.4%). Other than the greater incidence of gouty arthritis in the active treatment groups, there were no meaningful differences in the incidence of adverse events between placebo and the active controls.

During the open-label, long-term administration study, the most common adverse events in the overall dotinurad group were nasopharyngitis (17.9%), gouty arthritis (13.0%), arthralgia (4.8%), CPK increased (4.8%), and arthritis (4.5%).

4.2.3.2. United States Development Program (Phase 1 Study FBIO-DOT-101)

A small US-based Phase 1 study (FBIO-DOT-101) assessed the safety and tolerability of dotinurad doses (1, 2, 4, and 8 mg, vs placebo) in a 3-treatment period crossover study with healthy subjects. Subjects were randomized to sequence (placebo, 1 mg, and 4 mg, or, placebo, 2 mg, and 8mg), and treated with double-blind study medication for 4 days within each of the 3 treatment periods.

A total of N=15 healthy subjects were randomized (to sequence), with an average age of 35 years, 10 (66.7% male), 7 (46.7%) White and 7 (46.7%) Black or African American, with average BMI 26.3 kg/m^2.

Dotinurad was well-tolerated across the dose-range studied, with TEAEs only reported in the placebo and dotinurad 8 mg arms (Table 5). Safety outcomes were consistent with the Japanese database and supported initiation of this current Phase 1b study.

Table 5: Incidence of Treatment-Emergent Adverse Events in Phase 1 US Study of Dotinurad in Healthy Subjects (Study FBIO-DOT-101)

	Number (%) Subjects				
	Placebo	**Dotinurad 1 mg (N=7)**	**Dotinurad 2 mg (N=6)**	**Dotinurad 4 mg (N=6)**	**Dotinurad 8 mg (N=7)**
At least one TEAE	4 (28.6%)	0	0	0	3 (42.9%)
Serious TEAE	0	0	0	0	0
MedDRA Preferred Term					
SARS-Covid Positive Test	2 (14.3%	0	0	0	0
Headache	1 (7.1%)	0	0	0	1 (7.1%)
Acute Kidney Injury	1 (7.1%)	0	0	0	1 (7.1%)
Rash	1 (7.1%)	0	0	0	0
Rash popular	0	0	0	0	1 (7.1%)
Nausea	0	0	0	0	1 (7.1%)
Vomiting	0	0	0	0	1 (7.1%)

MedDRA = Medical Dictionary for Regulatory Activities Version 25.0; nS = number of subjects with an adverse event; N = number of subjects; TEAE = treatment-emergent adverse event; % = percentage of subjects with an adverse event (nS/N×100)

4.3. Rationale for this Study

Outcomes from this study will be used to determine the dose(s) of dotinurad to be used in the Phase 3 US-based development program. Data from this study may also be used to support the bridge to the Japanese data and therefore to support use of those Japanese data as part of a US-based regulatory package to support dotinurad as a treatment in the US. Data from this study, which includes a DDI component, will further provide data to allow for exploration of coadministration of dotinurad with allopurinol in larger efficacy/safety clinical trials.

Note that all patients in this study will be treated with open-label colchicine 0.6 mg once-daily (QD) for prophylaxis against gout, starting 14 days prior to randomization, and continuing daily open-label treatment with colchicine throughout the 7-day treatment (and through the last safety follow-up at Day 16).

5. TRIAL OBJECTIVES AND PURPOSE

This study has two objectives:

1. To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of 7 days of treatment with two doses of dotinurad monotherapy, and
2. To evaluate the effect of dotinurad, as monotherapy and in combination with allopurinol, versus allopurinol monotherapy, on the PK of each, and to assess the additive PD effects on serum uric acid and urinary urate excretion in U.S. patients with gout and hyperuricemia.

The safety/tolerability of each treatment (monotherapy dotinurad, combination of dotinurad and allopurinol, and monotherapy allopurinol) will also be assessed.

To achieve this objective, this study will evaluate the pharmacokinetics (PK), pharmacodynamics (PD), and safety/tolerability of 7 days of treatment with dotinurad monotherapy, followed by 7 days of treatment with concomitant allopurinol and dotinurad, and then followed by 7 days of treatment with allopurinol monotherapy. Two dose regimens of dotinurad (2 and 4 mg, once-daily) will be assessed in combination with allopurinol 300 mg once-daily.

Specific objectives include assessment of coadministration of dotinurad and allopurinol dosing over 7 days vs monotherapy dosing of each alone on:

- Pharmacokinetics (serum and urine);
- Uricosuric response (serum uric acid and urinary uric acid excretion);
- Safety and tolerability.

6. INVESTIGATIONAL PLAN

6.1. Study Design

This is a Phase 1B, open-label, 3-period, mulit-center multidose, PK/PD and drug-drug interaction (DDI) study. A total of N=20 eligible patients with gout and hyperuricemia will, following at least 14 days of washout of urate-lowering therapy (ULT) and open-label treatment with Colchicine 0.6 mg QD, be assigned (1:1) to one of 2 cohorts (N=10 patients each to the first cohort, dotinurad 2 mg, or to the second cohort, dotinurad 4 mg) and then treated with open-label study medication (given once-daily in the morning) for 7 days in each of 3 treatment periods (Table 6). Patients will continue with Colchicine 0.6 mg QD until the end of follow-up period.

Two doses of dotinurad (monotherapy and in combination with allopurinol) are being studied (dotinurad 2 mg and dotinurad 4 mg), with allopurinol 300 mg, with both medications given QD in the morning. Patients, Investigators and the Sponsor will not be blinded, and thus will be aware of the treatments given to each patient during each treatment period. Patients will be admitted to the CRU on the evening of Day -2 OR the morning of Day -1 to obtain baseline measurements for blood samples, a 24-hour urine collections (which will end shortly prior to the first dose of dotinurad on Day 1), and other scheduled assessments. Patients will remain in the CRU through the morning of Day 8, receiving daily morning doses of dotinurad on Days 1 through 7. Following the Day 7 dose, patients will undergo 24 hour serum and urine sampling, ending on the morning of Day 8 (prior to dosing with concomitant dotinurad and allopurinol). Patients will be discharged on the morning of Day 8, after having completed their PK and PD sampling procedures and after having received their first dose of treatment with concomitant dotinurad and allopurinol.

On Days 9, 10, 12, and 13, sites will conduct a daily telehealth visit (phone-call or video-call) to confirm that they have taken dotinurad with allopurinol and to provide a health check and reminder of hydration. On Day 11, patients will have a full safety laboratory assessment (in-clinic), which will include a serum creatinine test for renal function.

Patients will be re-admitted to the CRU on the evening of Day 13 OR early on the morning of Day 14. Following the Day 14 dose of concomitant dotinurad and allopurinol, patients will undergo 24 hour serial blood samples, 24-hour urine collections, and other scheduled assessments, ending on the morning of Day 15 (prior to dosing with allopurinol only). Patients will be discharged on the morning of Day 15 having completed their PK and PD sampling procedures and after having received their first dose of treatment with allopurinol monotherapy.

On Days 16 to 20, patients will conduct a daily telehealth visit to confirm that they have taken allopurinol and to provide a health check and reminder of hydration.

Patients will be re-admitted to the CRU on the evening of Day 20 OR early on the morning of Day 21. Following the Day 21 dose of allopurinol, patients will undergo 24 hour serial blood samples, 24-hour urine collections, and other scheduled assessments, ending on the morning of Day 22.

Patients will be encouraged to be well hydrated by consuming 2L of liquids a day during each day of the study. Patients will have a telephone follow-up on Day 28.

Table 6 provides the overall study design, cohort sequence of treatments, and the treatment periods during this study.

Table 6: Study Design, Cohort Sequence of Treatment, and Treatment Periods (Study UR1-DOT-103)

Screening (Days -28 to -15)	Washout of Prior Meds (Days -14 to -1)	Period 1 (Days 1 to 7) In-clinic	Period 2 (Days 8 to 14)	Period 3 (Days 15 to 21)	Follow-Up (Days 22 to 28)
	Colchicine 0.6 mg/day (can start any time at least 2 weeks prior to Day 1)				
Cohort 1	N=10 patients	Dotinurad 2 mg/day	Dotinurad 2 mg/day Allopurinol 300 mg/day	Allopurinol 300 mg/day	Follow-up period and scheduled telehealth call
Cohort 2	N=10 patients	Dotinurad 4 mg/day	Dotinurad 4 mg/day Allopurinol 300 mg/day	Allopurinol 300 mg/day	Follow-up period and scheduled telehealth call

6.2. Description of Study Periods and Procedures

The study has 5 general study periods:

1. Screening and washout
   - Screening (Days -28 to -1). Initial eligibility determination. Please note that if a patient is on urate lowering therapy (ULT) prior to screening, all other eligibility should be met during Screening period other than sUA. In these patients, the required fasting sUA level is =>8 mg/dl between Day -7 and Day -1. If a patient is not on ULT prior to Screening, the required fasting sUA level is =>8 mg/dl during Screening.
   - Washout of Uric-Acid-Lowering Drugs and Open-Label Treatment with colchicine 0.6 mg QD (Days -14 to -1 but can start as early as Day -28 if eligibility is confirmed at that time). Consent must be obtained prior to the start of washout of ULT and treatment with colchicine.
     – Treatments for the patients underlying gout/hyperuricemia (eg, allopurinol) will be reviewed at screening. All patients will be required to discontinue urate lowering medications at least 14 days prior to check in at the CRU on Day -1. Patients will also initiate treatment with open-label colchicine 0.6 mg QD (once daily each morning) at least 2 weeks (14 days) prior to check-in to the CRU. Colchicine is used for prophylaxis against gout flares during those 2 weeks while patients may be washing out of any other treatments for their underlying gout condition and will be continued throughout the study and follow-up period.
     – Importantly, initiation of colchicine treatment should be done at the same time the patient is washed out (ie, discontinues) any urate lowering medications, and can be up to 28 days prior to check-in at the CRU on Day -1.
2. Treatment period 1 (dotinurad monotherapy)

- Admission to CRU (evening Day -2 or early morning Day -1) and in-Clinic stay through the morning of Day 8.
- Day -1 to morning of Day 1: Confirmation of eligibility and final baseline/pre-treatment assessments. Collection of 24-hour urine collection.
- Days 1 through 7 In-Clinic Dosing with Dotinurad monotherapy
  - Open-label treatment each morning through Day 7 with dotinurad (2 mg for Cohort 1, 4 mg for Cohort 2)
  - Days 1, 4, and 7, following morning dose of dotinurad, 24-hour serum and urine collection for PK and PD
  - Days 2, 3, 5 and 6, trough samples (pre-dose) will be collected for serum PK and serum PD

3. Treatment period 2 (combination of dotinurad and allopurinol)
   - Discharge morning of Day 8 after pre-dose PK/PD sample collection and first dose with concomitant dotinurad (2 mg for Cohort 1, 4 mg for Cohort 2) and allopurinol 300 mg QD for all patients.
   - Period 2 (Days 9, 10, 11, 12, 13 Out-Patient Dosing with Concomitant Dotinurad/Allopurinol, Day 11 safety laboratory samples collected (in-clinic)
     - Open-label treatment continues each morning through Day 13. Telehealth visits (phone call or video-call) will be scheduled daily for confirmation of doses, a health check and a reminder for hydration.
     - On Day 11, patients will have a full safety laboratory assessment (in-clinic), which will include a serum creatinine test for renal function.
     - Check-in to CRU (evening of Day 13) OR early on the morning of Day 14
     - Day 14 morning dose with concomitant dotinurad (2 mg for Cohort 1 and 4 mg for Cohort 2) and allopurinol 300 mg QD for all patients and then 24-hour serum and urine collection for PK and PD through morning of Day 15
4. Treatment period 3 (allopurinol monotherapy)
   - Period 3 (Days 15 through 21) Out-Patient Dosing with Monotherapy Allopurinol
     - Discharge morning of Day 15 after pre-dose PK/PD sample collection and first dose with monotherapy allopurinol 300 mg. Open-label treatment continues each morning through Day 20. Telehealth visits will be scheduled daily for confirmation of doses, a health check, and a reminder for hydration.
     - Check-in to CRU (evening of Day 20) OR early the morning of Day 21
     - Day 21 morning dose with monotherapy allopurinol and then 24-hour serum and urine collection for PK and PD through morning of Day 22
5. End of Study follow-up period
   - End of Study Safety Follow-Up (Days 22 through 28)

  - Discharge morning of Day 22 after final PK/PD sample collection and safety assessments. Note that dosing with allopurinol is discontinued, with no dose given on Day 22.
  - Note that colchicine treatment will continue through the end of this safety follow-up period (Day 28). Patients are permitted to recommence their prior uric-acid-lowering medications during this follow-up period, under their physicians care and instruction.
- Final safety follow-up phone call on Day 28.

Table 7 provides the schedule of events.

Table 7: Schedule of Events (Study UR1-DOT-103)

Period:	**Screening**	**Baseline/Admission to the CRU**	**Treatment Periods (Days 1 through Day 21)**				**End of Study FU**
Day:	**-28 to -1**	**-2 or --1**	**Period 1 : Days 1-7 (In CRU Days 1 through 7)**	**Period 2: Days 8 to 14 (CRU Visit Days 11 and 14)**	**Period 3: Days 15 to 21 (CRU Visit Day 21)**	**Day 22**	**Day 28[1]**
Screening, consent	X						
Inclusion/Exclusion	X	X					
Medical history and screen for HLA-B*5801	X						
Prior/Con med check	X	X	X	X	X	X	X
COVID-19 testing	X	X		X (checkin)	X (checkin)		
Urine drug/alcohol/cotinine test	X	X					
Serology	X	X					
Body weight/height[2]	X	X					
Pregnancy test[3]	X	X			Pre-dose Day 15	X	
Serum uric acid eligibility	X						
Admission to clinic[4]		X (evening Day -2 or morning Day -1)		X (evening Day 13 or morning Day 14)	X (evening Day 20 or morning Day 21)		
Discharge from clinic				Morning Day 8	Morning Day 15	X	
Open-Label Study Treatment			Dotinurad (Days 1 to 7)	Dotinurad & Allopurinol (Days 8 to 14)	Allopurinol (Days 15 to 21)		
Washout of prior uric-acid lowering and treatment with Colchicine 0.6 mg/Day[8]	X (Days -14 to -1)	X	X	X	X		X
Physical examination[5]	X	X		Morning Day 8	Morning Day 15	X	
AE collection			X	X	X	X	X
Clin chem, hematology and urinalysis	X	X	Days 2, 4, 6	Day 8 pre-dose, Day 11 (any time), Pre-dose Day 14		X	
Lipid panel	X					X	
Coagulation	X	X				X	
Vital signs	X	X	Pre-dose daily	Pre-dose Day 14	Pre-dose Day 21	X	
ECG 12-lead	X	X	Pre-dose daily	Pre-dose Day 14	Pre-dose Day 21	X	
Blood samples for PK[6]			Days 1, 4, and 7: Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24h Days 3 and 6: Pre-dose	Day 14: Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24h	Day 21: Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24h		
Blood samples for PD (serum uric acid)	X	X	Days 1, 4, and 7: Predose, 2, 4, 6, 12, 24h	Day 14: Predose, 2, 4, 6, 12, 24h	Day 21: Predose, 2, 4, 6, 12, 24h		
Trough (pre-dose) blood samples for PD (serum uric acid) and PK			Days 2, 3, 5, and 6 (all pre-dose)				
24-hour urine[7] for PK and PD (urine dotinurad, creatinine, urate)		Day -1: 2, 4, 6, 12, 24h	Days 1, 4, and 7: 2, 4, 6, 12, 24h	Day 14: 2, 4, 6, 12, 24h	Day 21: 2, 4, 6, 12, 24h		

abbreviations: AE = adverse event; FU = follow-up visit; GFR = glomerular filtration rate; h = hour; PD = pharmacodynamics; PK = pharmacokinetics.
Note: Where assessments fall at the same timepoints, the order of priority is: dose administration , then PK blood samples, then any other assessments.

1. The follow-up visit will occur approximately 7 calendar days after discharge from the CRU via a scheduled telehealth phone call.
2. Height will be measured at screening only.

3. Pregnancy testing in females with child bearing potential; urine except for Day -1 which will be in serum. A positive urine pregnancy test must be confirmed with a serum pregnancy test.
4. Patients will be admitted to the clinic on the morning of Day -1 and will be discharged on the morning of Day 8. For periods 2 and 3, they are admitted either the evening before or the morning of the final dosing for each Period (eg, evening of Day 13 or morning of Day 14) and will remain resident until discharge the following morning after their Hour 24 serial blood samples and 24 hour urine collections for each Period.
5. Full physical examination at screening and Day -1; abbreviated (symptom-driven) physical examination at discharge for Day 8 and Day 15.
6. Predose PK draw to be collected within 30 minutes prior to first dosing at each period. Subsequent PK draws should be ±5 minutes of specified time for times up to 3 hours post dose and ±10 minutes thereafter.
7. Patients can urinate between the designated timepoints. Site will collect the urine sample and combine in the appropriate bins. Eg, Hour 0-2 means urine produced between hour 0 and hour 2. Precisely at hour 2, patients will be instructed to collect urine sample, with that sample stored in the Hour 0-2 container. For this study, the bins are 0-2, 2-4, 4-6, 6-12, 12 to 24 hours post dosing.
8. Colchicine treatment will start at the time patients start washout of their prior uric-acid-lowering medications (eg, allopurinol). This will be at least 14 days prior to starting treatment but can be longer (up to 28 days) at the discretion of the PI.

6.3. Number of Subjects

A total of N=20 patients will be assigned (N=10 to Cohort 1, dotinurad 2 mg, and N=10 to Cohort 2, dotinurad 4 mg). Patients discontinuing prematurely may be replaced at the discretion of the PI and Sponsor.

6.4. Treatment Assignment and Randomization

This is a Phase 1B study that assesses the PK and PD of dotinurad as well as the drug-drug interaction between dotinurad and allopurinol. The primary investigational product is dotinurad, while the coadministered product is allopurinol.

There are 2 dose levels of dotinurad to be studied:

- Dotinurad 2 mg QD
- Dotinurad 4 mg QD

Patients who meet eligibility criteria will be assigned in a 1:1 ratio (10 patients to each), in an open-label fashion, with the dotinurad 2 mg dose assigned to the first 10 patients, and the dotinurad 4 mg dose assigned to the second 10 patients, to treatment with one or the other dotinurad dose, and then treated sequentially in 3 periods (dotinurad monotherapy, coadministration of dotinurad and allopurinol 300 mg QD, and allopurinol monotherapy).

6.5. Criteria for Study Termination

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6.5.1. Temporary Halting and Stopping rules for Individual Subjects

If a subject experiences laboratory values that meet any of the following criteria, repeat tests will be performed (within ~24h of the reported value). If results continue to meet the criteria as described below, the PI, medical monitor and sponsor representative will review the results and subject's medical history and determine whether dosing of the subject can continue, should be temporarily suspended, or should be permanently discontinued.

- For liver function tests (LFTs):
  - Bilirubin 1.5-3.0x upper limit of normal (ULN) with no LFT elevation, or;
  - Bilirubin 1.26-1.5x ULN (with LFT elevation), or;
  - AST/ALT 3-5x ULN (with no elevation of total bilirubin (TBL).
- For kidney function tests:
  - Serum Creatinine (SCr) > 1.3X the average of the screening and baseline SCr.]

Treatment will be discontinued for an individual if any of the following are observed:

- ALT or AST > 5xULN;
- ALT or AST > 3xULN and (TBL > 2xULN or INR > 1.5);
- ALT or AST > 3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%);

SCr elevation > 1.5x the average of the subject's screening and baseline SCr values.

6.5.2. Stopping Rules for the Study

If the Sponsor, Investigator, or officials from the appropriate regulatory authorities discover conditions during the study that indicate the study should be terminated, this action may be taken after appropriate consultation between the Sponsor, PI and Medical Monitor. Conditions that may warrant termination of the study include, but are not limited to, the discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study including:

- An SAE considered related to study drug
- A major ECG finding considered related to the drug.
    - Major ECG findings include atrial fibrillation or flutter, high-degree atrioventricular dissociation, left bundle-branch block, right bundle-branch block, indeterminate conduction delay, isolated ischemic abnormalities, left ventricular hypertrophy with ST-T abnormalities, and other miscellaneous arrhythmias (e.g., supraventricular tachycardia, ventricular preexcitation, ventricular tachycardia. (Denes 2007).
- Two or more subjects receiving study drug who develop similar clinically significant laboratory abnormalities or other AEs indicating dose-limiting intolerance or severe adverse events in the same organ system.

The Sponsor reserves the right to terminate or suspend the study at any time; however, this should be discussed between the relevant parties beforehand and the reason for such decision recorded. Should this occur, all data available will also be recorded in the CRFs. The investigator should notify the relevant institutional IRB in writing of the study's completion or early discontinuation.

6.5.3. Early Termination

In the event that a subject ceases participation in the study or is withdrawn from the study by the PI prior to the end of treatment, the site will complete End of Study Procedure and Follow up Procedure. Every effort should be made to complete collection of data, see the SOE.

6.5.4. Patient Replacement

If, for reasons not related to safety or tolerability, it is not possible to obtain sufficient data from a cohort due to early withdrawal from the conduct of the study, additional subjects may, at the discretion of the PI and the Sponsor, be recruited.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject Inclusion Criteria

The following are subject inclusion criteria for this study; each subject must meet all inclusion criteria in order to be enrolled into this study.

Inclusion Criteria:

1. In the opinion of the investigator, the patient is capable of understanding and complying with protocol requirements.
2. Patients with a diagnosis of gout based on American College of Rheumatology criteria (1997). Patients must fulfill at least 3 of the following, with one of those 3 being (i) hyperuricemia.
    a. More than one attack of acute arthritis
    b. Maximum inflammation developed within 1 day
    c. Monoarthritis attack
    d. Redness observed over joints
    e. First metatarsophalangeal joint painful or swollen
    f. Unilateral first metatarsophalangeal joint attack
    g. Unilateral tarsal joint attack
    h. Tophus (proven or suspected)
    i. Hyperuricemia.
    j. Asymmetric swelling within a joint on x-ray
    k. Subcortical cysts without erosions on x-ray
    l. Monosodium urate monohydrate microcrystals on joint fluid during attack
    m. Joint fluid culture negative for organisms during attack
3. The patient signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures including requesting that a patient fast for any laboratory evaluations.
4. Negative COVID-19 test by either PCR or rapid antigen test at screening and check-in prior to first period, and agrees to be compliant with all COVID-19 measures mandated by the CRU prior to screening/entry into the trial.
5. Male or female between 18 and 75 years of age (inclusive). To be eligible, females can be either of NCBP (confirmed by surgical history, medical history of twelve consecutive months of amenorrhea, or FSH levels) or females of childbearing potential must be on a reliable method of birth control and also have a negative urine human chorionic gonadotropin (hCG) pregnancy test results on the Study Day -1.
6. Screening serum uric acid level of ≥7 mg/dl.
    a. If a patient is not on uric acid-lowering therapies (ULT) prior to screening, the required fasting sUA level is at least one ≥7 mg/dl during Screening
    b. If a patient is on ULT prior to screening, the required fasting sUA level is at least one =>7 mg/dl between Day -7 and Day -1

7. Screening liver enzymes (LFTs) <1.5x ULN. Total bilirubin ≤1x ULN. For patients with documented Gilbert Syndrome, total bilirubin ≤3 x ULN with direct bilirubin <1x ULN.
8. Screening renal function eGFR ≥ 60 mL/min/1.73m2.
9. Pre-dose hemoglobin should be within the normal range.
10. Body mass index (BMI) ≥ 18.5 and ≤ 40.0 (kg/m2) and a body weight of no less than 50 kg.
11. Medically healthy with no clinically significant screening results including but not limited to:
    a. Laboratory profiles other than sUA
    b. Urinalysis
    c. Vital signs
    d. Electrocardiograms (ECGs)
    e. Physical examination
12. No use of tobacco or nicotine containing products (including smoking cessation products), for a minimum of 3 months prior to dosing.

7.2. Subject Exclusion Criteria

The following are subject exclusion criteria for this study; each subject must **not** meet any of these exclusion criteria in order to be enrolled into this study.

1. The subject has current or historical evidence of any clinically significant disease or condition that might complicate the subject's participation, or, in the opinion of the Investigator, may place the subject at an unacceptable risk as a participant in this trial, may interfere with the interpretation of safety and/or tolerability data obtained in the trial, or may interfere with the absorption, distribution, metabolism, or excretion of the study drug.
2. Patients with unstable angina, New York Heart Association Class III or IV heart failure, myocardial infarction, stroke, or deep venous thrombosis within 1 year prior to Day 1.
3. QT interval corrected for heart rate according to Fridericia's formula >470 msec in females and >450 msec in males during Screening, confirmed by a repeat assessment.
4. History of or presence of kidney stones.
5. History of or presence of malignancy in the last 5 years other than treated cutaneous basal or squamous cell carcinoma.
6. Urological disorder not well controlled.
7. Peptic ulcer disease requiring active treatment.
8. Cannot safely discontinue uric acid-lowering medication 14 days prior to study start to 9 days after the last dose of study medication was administered.
9. Surgery within the past 90 days prior to dosing as determined by the Principal Investigator to be clinically relevant.

10. Use of agents that could confound serum uric acid analysis (eg, long-term use of salicylates >100 mg or use of losartan).
11. Patients with an acute gout flare during the screening period that had not resolved 1 week prior to the first dose of study.
12. Hypersensitivity or intolerance to allopurinol, dotinurad or colchicine.
13. Positive for HLA-B*58:01 allele
14. History or presence of alcoholism or chronic drug abuse within the past 2 years.
15. Psychiatric disorder or social situation that prevents compliance with the protocol.
16. Female patients who are pregnant or lactating.
17. Positive results for the urine drug /alcohol breath test/cotinine at check-in.
18. Positive results at screening for Human Immunodeficiency Virus (HIV), Hepatitis B Surface Antigen (HBsAg), Hepatitis C antibodies (HCV).
19. Patient's semi-recumbent blood pressure is less than 90/40 mmHg or greater than 155/90 mmHg during Screening and Day -1.
20. Stable dose of medications for long-term conditions such as diabetes, high cholesterol, hypertension, asthma, etc. are allowed (provided that the patient has been on a stable dose for at least 30 days prior to Screening and is not expected to require dose adjustment during the study through 7 days post study).
21. Patient reports receiving a strong or moderate inhibitor of CYP3A4 or a P-gp inhibitor within 1 month prior to study drug dosing, due to potential interactions with colchicine.
22. Patient has taken azathioprine, Imuran, or other medications that may interact with allopurinol within 1 month prior to study drug dosing
23. Participation in another clinical trial within 30 days of last IP administration or 5 half-lives (whichever is longer) of administration of any study drug evaluated in that trial prior to screening for this trial. Previous participation in a dotinurad trial is also exclusionary.

7.3. Subject Withdrawal Criteria

If a subject is discontinued from the study prematurely, the Investigator must select the primary reason for discontinuation on the End of Study eCRF. In addition, every effort should be made to complete the assessments listed under Discharge Day 13 on the Schedule of Assessments for each dosed subject.

Subjects withdrawn from the study will be considered evaluable for statistical assessment.

A subject may be removed from the study for the following medical or administrative reasons:

- Adverse Event: If a subject experiences an adverse event that the subject finds unacceptable or that, in the judgment of the Investigator or the Medical Monitor presents an unacceptable consequence or risk to the subject, the subject may be discontinued from further participation in the study.

- Administrative Discontinuation: After consultation with the Investigator or Medical Monitor, a subject may be discontinued from the study for failure to comply with protocol requirements. All instances of noncompliance must be documented in the eCRF.
- Refusal of Assessments: If for any reason, following dosing, the subject refuses further assessment during the study, the subject shall be discontinued from the study and the reasons for refusal documented. Reasonable efforts shall be made to monitor the subject for adverse events following such discontinuation. Such efforts shall be documented.

8. TREATMENT OF SUBJECTS

Total patient participation in this study, from initial screening through the final assessment, is expected to be approximately 7 to 8 weeks per individual. Total time in-clinic is expected to be approximately 10 days (from admission evening Day -2 or morning Day -1 through discharge morning Day 8, and then again Day 14 through morning of Day 15, and Day 21 through morning Day 22). Patients may check in the evening before (ie, Day -2, Day 13, and Day 20) at the discretion of the clinic.

Patients in this study will be required to be treated with colchicine, dotinurad (the investigational product), and allopurinol (for with the DDI assessment will be made).

8.1. Open-Label Colchicine

All patients will be required to initiate treatment with open-label colchicine 0.6 mg QD (once daily each morning) at least 2 weeks (14 days) prior to Period 1 check-in (Day -2 or -1) to the CRU. Colchicine is used for prophylaxis against gout flares during those 2 weeks while patients may be washing out of any other treatments for their underlying gout condition. Initiation of colchicine treatment should be done at the same time the patient is washed out (ie, discontinues) any uric-acid-lowering medications (eg, allopurinol), and can be up to 28 days prior to check-in at the CRU on Day -2 or Day -1.

Colchicine use will continue through the patient discharge (Study Day 22) and may continue through Day 28. Note that on days where patients are taking both colchicine and study medication, patients may take the medications at different times of the morning or all at the same time, at the patients convenience.

8.2. Description of Study Drugs

While the primary investigational product is dotinurad, all patients will also receive treatment with allopurinol.

Study drugs will be distributed to the clinic using a designated distribution center. The Sponsor will provide the investigator with adequate quantities of investigational product and supplies to conduct the study. Specific details regarding investigational product supplies, dose preparation, and accountability will be described in a pharmacy manual at the clinic.

Table 8 provides a summary description of the drug products, including the dosage form, the unit dose, and a physical description of the product.

Table 8: Investigational Products (Study UR1-DOT-103)

	Investigational Product	
Product Name:	Allopurinol	Dotinurad
Dosage Form:	tablet	tablet
Unit Dose:	300 mg	1 mg
Route of Administration:	Oral	Oral
Physical Description:	white, round	White, round
Manufacturer:	Various	Fuji Yakuhin Co. Ltd

8.3. Treatments to be Administered

Study drug (dotinurad and allopurinol) will be administered in an open-label fashion. Dotinurad will be given as 1 mg pills, while allopurinol will be given as 300 mg tablets.

The dose administered to each patient on each dosing day will follow the scheme described in Table 9. Treatment will be given orally once-daily in the morning. Dosing occurs each day, approximately 30 minutes after finishing breakfast. The study drug will be administered with approximately 240 mL of water. Patients are required to eat a breakfast and requested to drink at least 2 Liters of water/fluids per day to ensure hydration throughout the course of the study.

Table 9: Dotinurad Tablet allocation by Treatment Assignment (Study UR1-DOT-103)

Cohort	Daily dose of Dotinurad	Number of Dotinurad tablets (each tablet is 1 mg)
1	2 mg	2
2	4 mg	4

8.4. Concomitant Medications (including Uric-Acid Lowering Medications)

All medications including over-the-counter medications and herbal supplements taken during the 30 days prior to the first study drug administration will be recorded and reviewed by the PI to determine whether the participant is suitable for inclusion. Any uric-acid-lowering medications (eg, allopurinol) will be discontinued at least 14 days prior to check-in on Day -2 or Day -1.

Stable dose of medications for long-term conditions such as diabetes, high cholesterol, hypertension, asthma, etc. are allowed provided that the patient has been on a stable dose for at least 30 days prior to Screening and will not require dose adjustment during the study through 7 days post study.

Prior therapy (after randomization/enrollment) or concurrent therapy (after start of study drug) with any medications, including both prescription and nonprescription drugs (except in the case

of necessary treatment of AEs), should first be discussed with the Investigator and Sponsor's Medical Monitor before study drug administration, unless appropriate medical care necessitates that therapy should begin before the Investigator and Sponsor's Medical Monitor can be consulted. However, paracetamol/acetaminophen up to a maximum daily dose of 2 grams may be used for minor ailments during the course of the study without prior consultation with the Sponsor's Medical Monitor.

NSAIDS may be used for the treatment of gout flare as per the specific labels. Alternately, increased dose of colchicine to 0.6 mg bid may be used if this is the site standard of care for treating gout flares. Other analgesics such as opioids may also be considered. Subjects should be encouraged to continue in the study if possible.

Due to potential interactions with colchicine, any use of moderate to strong Cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) inhibitors within 1 month prior to study drug dosing throughout the study is prohibited. Moderate to strong CYP3A4 inhibitors are as follows (this listing is not all inclusive): atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, and verapamil, P-gp inhibitors include cyclosporine and ranolazine.

Due to potential interactions with allopurinol use of azathioprine, Imuran or other drugs known to interact with allopurinol should be avoided.

A full list of interactions can be found at https://drug-interactions.medicine.iu.edu/maintable.aspx

Any medications including over-the-counter medications and herbal supplements (other than study drug) taken by participants during the course of the study will be recorded. Concomitant medications will be recorded by their generic name.

Concomitant medications will be coded using the WHO Drug Dictionary.

8.4.1. Washout of Uric-Acid-Lowering Medications

Treatments for the patients underlying gout/hyperuricemia will be reviewed at screening. All patients will be required to discontinue uric-acid-lowering medications at least 14 days prior to check in at the CRU on Day -2 or Day -1. Patients will also initiate treatment with open-label colchicine 0.6 mg QD (once daily each morning) at least 2 weeks (14 days) prior to check-in to the CRU. Colchicine is used for prophylaxis against gout flares during those 2 weeks while patients may be washing out of any other treatments for their underlying gout condition.

Importantly, initiation of colchicine treatment should be done at the same time the patient is washed out (ie, discontinues) any uric-acid-lowering medications, and can be up to 28 days prior to check-in at the CRU on Day -1. Treatment with colchicine will continue through the course of the 3 treatment periods.

8.5. Treatment Compliance

Treatment compliance with study medication during the treatment periods is expected to be high. The date and time of study drug administration will be recorded on the eCRF.

8.6. Diet, Hydration, Physical Activity, and Other Restrictions

Study medication treatment (dotinurad and/or allopurinol) will be given orally once-daily in the morning. Dosing occurs from Day 1 to Day 21 at approximately 30 minutes after finishing breakfast. Study drugs will be administered with approximately 240 mL of water. Patients are required to eat a breakfast and drink at least 2 Liters water/fluids per day to ensure hydration.

- Alcohol: participants will refrain from consumption of alcohol for 24 hours before study drug dosing and check-in to the CRU on Day -1. Alcohol is not permitted in the CRU. During the study period, alcohol is not permitted. Alcohol is a diuretic and thus should be considered in the context of patients remaining adequately hydrated.
- Grapefruit juice: Consumption of grapefruit juice is prohibited throughout the study.
- Hydration: Patients will be encouraged to remain hydrated by drinking approximately 2 liters of fluids per day while participating in the trial starting at Day -1 through Day 22.
- Caffeine: up to two (2) 6-oz cups are allowed per day during Day -1 to Day 22
- Cigarettes and other nicotine containing devices: smoking and vaping are not permitted during the study (from Screening to Last Visit).
- Strenuous exercise: participants will avoid *unaccustomed* strenuous physical activity (e.g., weight lifting, running, bicycling) during the study. During the study period, strenuous unaccustomed exercise is not permitted.

8.7. Randomization, Blinding and Unblinding

This is an open-label (non-randomized) study. Patients, investigational staff (including the PI), the Sponsor, and other study personnel will be aware of the treatments being given to the patients. Because the primary objectives of this study are focused on PK and PD assessments, all measured by serum and urine sampling (and thus are objective), open-label treatment is scientifically reasonable.

9. STUDY DRUG MATERIALS AND MANAGEMENT

Study drug (dotinurad and allopurinol) will be provided to the clinic for each of the treatment groups. Colchicine will be prescribed by the sites for patients to obtain from their local (home) pharmacy.

9.1. Study Drug Packaging and Labeling

Study drug will be provided to sites in labeled bottles. The pharmacy manual will describe this in more detail.

9.2. Packaging, Labeling, and Storage of Clinical Supplies

Investigational products are for investigational use only and the study drug supplied for this study is intended for use only within the context of this study. The study drug supplied for this study should be stored in a secure place until dispensed for patient use or returned to the Sponsor.

Investigational products should be stored at room temperature (20 to 25°C or 68 to 77°F); limited excursions to 15°to 30°C (59°to 86°F) are permitted. Investigational products should be stored away from heat sources and direct sunlight.

The Investigator, pharmacist, or their designee, will verify that study drug supplies are received intact and in the correct amounts by signing and dating the investigational product receipt log. The person receiving the supplies must verify that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable drug in a given shipment will be documented in the study files. The Investigator must notify the Sponsor or designee of any damaged or unusable investigational product supplied to the Investigator's site.

The site will maintain a Drug Inventory Log (includes, but not limited to, the following: lot number, number of units received and number of tablets dispensed). The site will also maintain patient-specific drug dispensing logs.

An overall accountability of investigational product will be performed and verified throughout the study and at the site closeout visit. Upon completion of the study, copies of the investigational product accountability records will be returned to the Sponsor. All used and unused study drug supplies will be inventoried, accounted, and returned to the Sponsor or designee at the end of the study. By signing the Investigator Agreement page of this protocol, the investigator or named sub-investigator agrees not to supply study drug to any person(s) not enrolled in the study.

9.3. Study Drug Preparation

Study drug will be dispensed by the qualified, licensed study personnel and administered to the patient by a licensed designated staff member. The designated personnel will prepare the treatments for administration and maintain accountability records. Study treatment for each period will be prepared according to the treatment assignments.

9.4. Study Drug Accountability

During in-clinic study days, subjects will be treated at the investigational center and therefore the Pharmacist or other investigational staff via documentation of receipt of the study drug and dosing/treatment given will perform drug accountability. Note that because this study also includes out-patient dosing, the sites will confirm consumption of morning doses of dotinurad and/or allopurinol at check-in at the start of Periods 2 and 3. Further, on Days 9, 10, 12, and 13, sites will conduct a daily telehealth visit (phone-call or video-call) to confirm that they have taken dotinurad with allopurinol and to provide a health check and reminder of hydration.

9.5. Study Drug Handling and Disposal

Details regarding study drug handling and disposal are provided in the site Pharmacy Manual.

Records of receipt, dispensing records and inventory forms, as applicable, will be examined and reconciled during and at the end of the study. Both the investigational drug that is used during the course of the study, as well as any remaining unused investigational drug, must be accounted for on a drug accountability record provided to the PI by the Sponsor or its designee. Drug destruction will be completed following CRO SOP on destruction and a destruction certificate will be maintained at the clinic.

If directed, at the end of the study, all unused investigational drug, accompanied by a packing slip, must be returned. Return information will be provided to the sites.

In addition, a copy of all completed drug accountability records must be retained in the Investigators' Study Files, with a copy sent to the Sponsor or its designee.

The products are to be stored in a safe place (locked facility) at the appropriate temperature and without exposure to freezing.

10. PHARMACOKINETIC AND PHARMACODYNAMIC SAMPLING ASSESSMENTS

This study has two objectives:

1. To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of 7 days of treatment with two doses of dotinurad monotherapy, and
2. To evaluate the effect of dotinurad, as monotherapy and in combination with allopurinol, versus allopurinol monotherapy, on the PK of each, and to assess the additive PD effects on serum uric acid and urinary urate excretion in U.S. patients with gout and hyperuricemia.

For the first objective, the following PD and PD assessments will be included.

- PK assessment will be performed of dotinurad in both serum and urine. Plasma and urine sample collection will be performed throughout the course of the treatment period, with more intensive sampling on Days 1, 4, and 7. PK parameters will include (but are not limited to) AUC and Cmax (see the protocol body for the full list of parameters to be estimated). Attainment of steady state will be assessed for dotinurad using Helmert Contrasts on the trough concentrations from Days 2 through 8.
- PD assessments include serum uric acid lowering and urine urate excretion increase versus pretreatment. detailed assessments of these endpoints will be pretreatment and then Day 1, 4, and 7. PD endpoints will include area under the effect-time curve (AUEC) and maximum observed response (Emax), as well as fractional excretion of urate.

For the second objective, the following PK and PD assessments will be included.

- PK assessment of dotinurad, allopurinol, and oxypurinol after an oral dose on the 7th day of each treatment period will be determined for each treatment. Plasma PK parameters will include (but are not limited to) AUC and CMax (see the protocol body for the full list of parameters to be estimated). Urine PK parameters will include (but are not limited to) the amount excreted amount in urine (Ae) and the fractional excretion of uric acid in urine (as a function of the total dose amount) (fe). The study will assess how the co-administration of dotinurad and allopurinol impacts the exposure level of the two drugs as compared to monotherapy.
- PD assessments of serum uric acid lowering and urine urate excretion observed on the combination therapy versus each monotherapy on the 7^{th} day of each treatment period will be determined. PD parameters will include uric acid area under the effect-time curve (AUEC) and maximum observed response (Emax). PD parameters, such as time-matched percentage change on the steady-state day (end of each treatment period) from baseline for sUA, urinary urate excretion (mg), and fractional excretion of urate will be calculated.

Use of two dose levels of dotinurad will also allow for assessment of dose-response.

Details regarding the sample collection for these PK and PD endpoints are included in the sections below.

10.1. Blood Sample Collection for PK and PD

This study will include 5 days of serial blood sampling for pharmacokinetic analysis (dotinurad, as well as allopurinol and oxypurinol) as well as trough sampling (Period 1 only), collected at the following time points.

Period 1 (dotinurad)

- Study Day 1: Predose, and post-dose at Hours 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 (+5 min)
  - Study Day 2: Trough, Hour 24 from Day 1 predose (immediately pre-dose) (+10 min)
  - Study Day 3: Trough, Hour 48 from Day 1 predose (immediately pre-dose) (+10 min)
- Study Day 4: Predose, and post-dose at Hours 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 (+5 min)
  - Study Day 5: Trough, Hour 24 from Day 4 predose (immediately pre-dose)(+10 min)
  - Study Day 6: Trough, Hour 48 from Day 4 predose (immediately pre-dose) (+10 min)
- Study Day 7: Predose, and post-dose at Hours 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 (+5 min)
  - Study Day 8: Trough, Hour 24 from Day 7 predose (immediately pre-dose) (+10 min)

Period 2 (dotinurad, allopurinol, and oxypurinol)

- Study Day 14: Predose, and post-dose at Hours 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 (+5 min)
  - Study Day 15: Hour 24 from Day 15 predose(immediately pre-dose) (+10 min)

Period 3 (allopurinol and oxypurinol)

- Study Day 21: Predose, and post-dose at Hours 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 (+5 min)
  - Study Day 22: Hour 24 from Day 22 predose(immediately pre-dose) (+10 min)

Similarly, this study will include 5 days of serial blood sampling for pharmacodynamic analysis (serum uric acid) as well as trough sampling (Period 1 only), collected at the following time points.

Screening

- Screening
- Day -1 (morning at approximately the expected ‘predose’ timepoint)

Period 1

- Study Day 1: Predose, and post-dose at Hours 2, 4, 6, and 12 (+5 min)
  - Study Day 2: Trough, Hour 24 from Day 1 predose (immediately pre-dose) (-10 min)
  - Study Day 3: Trough, Hour 48 from Day 1 predose (immediately pre-dose) (-10 min)
- Study Day 4: Predose, and post-dose at Hours 2, 4, 6, and 12 (+5 min)
  - Study Day 5: Trough, Hour 24 from Day 4 predose (immediately pre-dose) (-10 min)
  - Study Day 6: Trough, Hour 48 from Day 4 predose (immediately pre-dose) (-10 min)
- Study Day 7: Predose, and post-dose at Hours 2, 4, 6, and 12 (+5 min)
  - Study Day 8: Trough, Hour 24 from Day 7 predose (immediately pre-dose) (-10 min)

Period 2

- Study Day 14: Predose, and post-dose at Hours 2, 4, 6, and 12 (+5 min)
  - Study Day 15: Hour 24 from Day 15 predose (immediately pre-dose)

Period 3 (-10 min)

- Study Day 21: Predose, and post-dose at Hours 2, 4, 6, and 12 (+5 min)
  - Study Day 22: Hour 24 from Day 22 predose (immediately pre-dose) (-10 min)

10.2. Serum PK and PD Sample Handling and Shipping

All tubes must be labeled such that the protocol number, site number, subject number, date and protocol (nominal) time the specimen was collected can be verified. It is important to note the exact actual date and time of the blood collection on the eCRF, not just the protocol specified (nominal) time. Labels will be fixed to freezing tubes in a manner that will prevent the label from becoming detached after freezing.

A laboratory manual will describe sample handling. Generally, samples will be sequentially collected by direct venipuncture and processed in a timely manner. All blood samples will be stored on ice or at 4°C for no more than 30 minutes until plasma is harvested. Blood samples will be centrifuged in a refrigerated centrifuge (approximately 4°C) at 3000 rpm for 10 minutes. The harvested plasma will be split into two approximately equal aliquots and stored in 2 mL or appropriate size cryovial tubes in a freezer pending shipment for drug analysis. The plasma samples will be frozen within approximately 60 minutes of harvesting. Samples (one aliquot of each sample) will be shipped and analyzed at the bioanalytical laboratory. The second aliquot of each sample may be shipped to the bioanalytical laboratory following confirmation of receipt of all samples from the first aliquot shipment.

10.3. Urine Sample Collection for PK and PD

A laboratory manual will describe urine sample handling. Generally, urine collection for both PK and PD analysis will be based on 24-hour collection intervals. Aliquots of urine will be obtained after collection and measurement of interval excretion volume (which will be determined by weight). Samples will be stored at -80°C (±10°C) prior to analysis. The pharmacokinetics of dotinurad in urine will be evaluated.

Urine samples (24-hour collection) will be collected according to defined time interval 'bins'. Collection times will have a window of +10 minutes. Collection days and time bins are as follows:

Screening

- Day -1 (starting at approximately the expected 'predose' timepoint), collection bins Hours 0 to 2, Hours 2 to 4, Hours 4 to 6, Hours 6 to 12, and Hours 12 to 24 (ending immediately prior to Day 1 start of study drug dosing)

Period 1

- Day 1 collection bins Hours 0 to 2, Hours 2 to 4, Hours 4 to 6, Hours 6 to 12, and Hours 12 to 24 (ending immediately prior to Day 2 study drug dosing)
- Day 4 collection bins Hours 0 to 2, Hours 2 to 4, Hours 4 to 6, Hours 6 to 12, and Hours 12 to 24 (ending immediately prior to Day 5 study drug dosing)
- Day 7 collection bins Hours 0 to 2, Hours 2 to 4, Hours 4 to 6, Hours 6 to 12, and Hours 12 to 24 (ending immediately prior to Day 8 study drug dosing)

Period 2

- Day 14 collection bins Hours 0 to 2, Hours 2 to 4, Hours 4 to 6, Hours 6 to 12, and Hours 12 to 24 (ending immediately prior to Day 15 study drug dosing)

Period 3

- Day 21 collection bins Hours 0 to 2, Hours 2 to 4, Hours 4 to 6, Hours 6 to 12, and Hours 12 to 24 (morning of Day 22)

Urine collection bins are to be collected strictly in the time intervals defined. For instance, the "Hour 0 to 2" interval (post-dose) is intended to collect all urine produced during that time.

- Patients will collect any void during the time interval and will be instructed to collect a void/urine immediately prior to Hour 2 post-dose. If a patient cannot void at the end of the interval this should be noted and the interval completed.
- Any urine collected between Hour 0 and Hour 2 will be stored in a specific container JUST FOR THAT TIME INTERVAL.

For the Hour 2 to 4 bin, patients will be instructed to provide a urine sample immediately prior to Hour 4.

- Any urine collected between Hour 2 and Hour 4 will be stored in a specific container JUST FOR THAT TIME INTERVAL.

The collection and storage of urine samples by these predefined bins, using specific containers for each interval accordingly, will continue through 24 hours post-dose.

An aliquot of urine will be obtained from each interval collection's bin after it has been mixed and weighed, and will be transferred to a labelled sample tube and stored at 4°C (±10°C) prior to analysis. The volume of urine in each interval will be determined by weight.

10.4. Urine Sample Handling and Shipping

The clinical staff will inventory the samples which are to be shipped to the bioanalytical laboratory.

For sample shipment requiring a third party courier, the samples will be packed in ample dry ice within a Styrofoam container to ensure the samples will remain frozen for at least 72 hours and shipped via express delivery to the bioanalytical facility. Written notification of sample shipment will be communicated to the bioanalytical facility. The samples will be tracked to assure arrival in a safe and timely manner.

The shipment will be accompanied by logs showing the name of the study drug product, the protocol number, and the subjects and samples included in the shipment. Documentation noting the conditions of the samples upon arrival at the bioanalytical laboratory and whether the amount of dry ice remaining is adequate or inadequate should be returned to the clinic.

11. ASSESSMENT OF SAFETY

11.1. Safety Parameters

Safety assessments will include collection of adverse events. In addition, safety assessments include clinical laboratory tests, vital signs, physical examination, and 12-lead ECGs.

11.1.1. Demographic/Medical History

Demographic information and medical history will be collected at Screening for determination of eligibility.

11.1.2. Vital Signs

Vital sign assessments include blood pressure, pulse, oxygen saturation, temperature and respiratory rate and are collected at varied times as per the Schedule of Events. Subjects will have vital signs taken in the seated position after 2 minutes rest. Blood pressure is repeated at specific timepoints. A window of +5 minutes will be allowed for vital signs.

11.1.3. Weight and Height

Height and weight will be captured as per the Schedule of Events.

11.1.4. Electrocardiogram (ECG)

All scheduled ECGs will be performed after the subject has rested supine for approximately 5 minutes. Whenever 12-lead ECGs are scheduled to occur at the same nominal time as a blood draw or vital sign measurement, the order of assessments will be PK, then ECG then vital signs.

11.1.5. Physical Examination

A physical examination will be conducted and abnormalities will be described. At times indicated in the Schedule of Events, only symptom-driven examinations will be performed.

11.1.6. Laboratory Assessments

All laboratory assessments will be collected as per the schedule of events.

11.1.6.1. Laboratory Collection, Including Hematology, Chemistry, Urinalysis, Coagulation, Serology, Pregnancy, and Drug Screens

Laboratory samples will be collected per the schedule of events, with the following analytes and tests assessed:

- Hematology: Red blood cells (RBC), White blood cells (WBC) (absolute counts and differential), Hemoglobin, Hematocrit, Platelets.
- Serum Chemistry: ALT, Albumin, Alkaline phosphatase, AST, Bilirubin (total and direct), Total protein, Creatinine, Uric acid, Blood urea nitrogen, Creatine kinase, gamma-Glutamyl transferase, Potassium, Sodium, Glucose, Chloride, Bicarbonate, Calcium. eGFR will be provided as part of the serum chemistry.

- Urinalysis: pH, Specific gravity, Protein, Glucose, Blood, Nitrite, Leukocyte esterase, Ketones, Bilirubin, Urobilinogen
- Coagulation: PT/INR, aPTT
- Serology diagnostic screening: HIV test, Hepatitis panel, including HBsAg and anti-HCV
- Female patients: serum hCG and or FSH, urine hCG
- Drug screen: amphetamines, barbituric acids, benzodiazepines, cannabinoids, cocaine, opiates, and cotinine.
- Breath alcohol test
- Covid-19 testing (prior to admission into CRU each Period)

11.2. Adverse and Serious Adverse Events

11.2.1. Definition of Adverse Events

11.2.1.1. Adverse Event (AE)

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Adverse events may include safety findings considered to be clinically significant by the Investigator. An adverse drug event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not it is related to the medicinal product. Reporting an adverse event does not necessarily reflect a conclusion by the Investigator that the event is causally related to the drug.

All adverse events should be captured and documented along with any supporting documentation. Adverse events should be spontaneously reported or elicited by non-suggestive probing. Signs or symptoms associated with a worsening in either severity or frequency as compared to a baseline condition should be evaluated by the Investigator for clinical significance and adverse event reporting.

Each adverse event in this study will be assessed for Grade, where Grade of an AE refers to the severity of the AE. Grade will be assessed according to CTCAE Version 4.03 or higher. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE that are based on this general guideline. Table 10 provides the CTCAE grades and grade descriptions to be used in this study.

For this study adverse Events collection will begin once the patient has begun colchicine pre-treatment. Any adverse events that occur prior to the first dose of study drug will be considered pre=treatment events and events that happen post first study drug dose will be considered treatment ermergent events.

Table 10: CTCAE Grade (Study UR1-DOT-103)

CTCAE Grade	CTCAE Grade Description
Grade 1: Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2: Moderate	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[1].
Grade 3: Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[2].
Grade 4: Life-threatening	Life-threatening consequences; urgent intervention indicated.
Grade 5: Death	Death related to the AE

Activities of Daily Living (ADL)
[1] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[2] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03 will be used for AE grading. A complete CTCAE list can be downloaded at http://evs.nci.nih.gov/ftp1/CTCAE/About.html.

11.2.1.2. Serious Adverse Event (SAE)

A serious adverse event is an AE occurring during the study, and at any dose of the investigational product, that fulfills one or more of the following:

- Results in death
- It is immediately life-threatening
- It requires in-subject hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

Reporting serious adverse events requires additional detailed reports and follow-up, depending upon the Investigator's estimate of a causal relationship between the test agent and the adverse event(s), and whether the adverse event(s) is identified in nature, severity, and frequency in the Investigator's Brochure or other risk information supplied to the Investigator.

All serious adverse events (SAEs) should be submitted promptly to the Institutional Review Board/Independent Ethics Committee (IRB/IEC). The investigator must make an effort to obtain all hospital medical records including discharge summary confirming final diagnosis. The death of a subject must be immediately (within 24 hours) reported to the IRB. All serious and non-

serious adverse events should be thoroughly documented and followed out by the Investigator until the event resolves or until discharge. The event may be followed longer, if deemed necessary. For any death occurring during the trial, the medical condition that led to the death should also be noted. The "outcome" status should be noted as "death" in these cases of SAEs that resulted in death. In addition, all SAEs that occur within 1 week following discharge or early termination visit should be recorded and reported as noted previously.

11.3. Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE. The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. For purposes of the definitions below, "temporal sequence" is defined as an association between administration of a drug and the observed reaction or event such that the drug was present prior to the reaction or event.

DEFINITE - The adverse event:

- follows a reasonable temporal sequence from drug administration,
- abates upon discontinuation of the drug (dechallenge), AND
- is confirmed by reappearance of the reaction on repeat exposure (rechallenge).

PROBABLE - The adverse event:

- follows a reasonable temporal sequence from drug administration,
- abates upon discontinuation of the drug (dechallenge), and
- Cannot be reasonably explained by the known characteristics of the subject's clinical state.

POSSIBLE - The adverse event:

- follows a reasonable temporal sequence from drug administration, and;
- Could have been produced by the subject's clinical state or by other modes of therapy administered to the subject.

REMOTE

- The temporal sequence between the adverse event and the drug administration is such that the drug is not likely to have had any reasonable association with the observed event.

DEFINITELY NOT – The adverse event:

- is definitely produced by the subject's clinical state or by other modes of therapy administered to the subject.

11.4. Recording Adverse Events

Adverse events spontaneously reported by the subject/caregiver and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at

the investigational site. Information about treatment-emergent AEs will be collected from dosing of the study drug through discharge, pre-treatment AE's will be collected from the start of colchicine until the first dose of study medication. SAEs occurring within 1 week of discharge/ET will also be reported. The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), severity, causality, action taken, serious outcome (if applicable), and whether or not it caused the subject to discontinue the study.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 11.2.1.2. An AE of severe intensity may not be considered serious.

Should a pregnancy occur, it must be reported and recorded on a pregnancy reporting form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

11.5. Reporting Serious Adverse Events

All SAEs (related and unrelated) will be recorded from the first administration of study drug until discharge. Any SAEs considered at least possibly related to the investigational product and discovered by the Investigator at any time after the study should be reported. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents.

Additional follow-up information, if required or available, should all be communicated within one business day of receipt and this should be completed on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the eCRF and/or study file.

The Sponsor is responsible for notifying the relevant regulatory authorities of certain events. It is the Investigator's responsibility to notify the IRB of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical trial. Each site is responsible for notifying its IRB or IEC of these additional SAEs.

12. STATISTICS

The statistical methods to be used in the analysis are consistent with both the study design and the study objectives. A detailed statistical analysis plan (SAP) will be written; that SAP will describe, in detail, the methods to be used and will provide table, listing, and figure 'shells' that will demonstrate what those outputs will look like.

Note that the overarching objective is to identify dose(s) to carry forward into Phase 3. To that end, the analysis will be structured to allow for review of dose proportionality and dose response (eg, on PD endpoints, vis-à-vis the number (%) of patients responding on serum uric acid by various response definitions). The use of graphics will be extensive in presenting the outcomes across the PK and PD endpoints.

12.1. Sample Size Considerations

A sample size of n=10 patients per dotinurad dose level is sufficient to determine whether a PK or PD difference exists for those endpoints (both as a monotherapy and coadministered with allopurinol). This is based on observed coefficients of variation of PK parameters for prior dotinurad studies, as well as previous publications of similar studies with allopurinol (see Baumgartner 2018).

Further, studies of dotinurad in Japanese patients have demonstrated low variability of PK and PD endpoints and have therefore required a small number of patients to demonstrate clear study outcomes. This is based on observed coefficients of variation of PK parameters for prior dotinurad studies. Specifically, studies of dotinurad in Japanese patients have demonstrated low variability of PK and PD endpoints and have therefore required a small number of patients to demonstrate clear study outcomes.

For instance, Study FYU-981-012 demonstrated (Table 11), with 7 days of dosing with dotinurad 4 mg, coefficients of variation (CV%) (defined as the standard deviation divided by the mean, x 100) for Day 7 Cmax of 12.9%, and Day 7 AUC(0-24) of 12.2%, which are extremely low measures of variability in PK assessment.

Table 11: PK parameters of plasma FYU-981 concentration of repeated oral administration of Dotinurad 4 mg (Japanese Study FYU-981-012)

	Dotinurad group					
	Treatment Day 1		Treatment Day 4		Treatment Day 7	
	Subjects (n)	Mean ± SD	Subjects (n)	Mean ± SD	Subjects (n)	Mean ± SD
C_{max} (ng/mL)	6	366.50 ± 81.19	6	416.33 ± 77.74	6	420.67 ± 54.21
T_{max} (hr)	6	3.33 ± 0.52	6	2.67 ± 1.21	6	3.17 ± 0.75
$T_{1/2}$ (hr)	6	11.14 ± 1.56	6	11.27 ± 1.22	6	9.87 ± 1.20
AUC_{0-24} (ng·hr/mL)	6	4024.16 ± 758.92	6	5052.31 ± 1073.14	6	4871.26 ± 890.21
AUC_{0-inf} (ng·hr/mL)	6	5357.79 ± 1255.76	6	6690.02 ± 1581.48	6	6099.16 ± 1339.18

Based on these outcomes, as well as preliminary data from the recently-completed Phase 1 US-based study (FBIO-DOT-101), in which clear dose-response was evident with n=7 subjects per treatment arm, provide justification for the sample size in this current study.

12.2. General Statistical Methods

Listings will be provided for all data captured in the database. Listings will include all subjects assigned to the patient population and include data up to the point of study completion or discontinuation. Patients are generally considered to have completed the study if they complete the scheduled follow-up visit (rather than early termination visit). Any subject who discontinues the study will be identified accordingly in the listings. Summaries and statistical analyses will include the subjects assigned to the relevant population based on data type.

Data analysis will be performed using the SAS® statistical software package Version 9.4 (or higher).

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) ADaM Version 2.1 (or higher if a new version is issued during the study) and CDISC ADaM Implementation Guide Version 1.1 (or higher if a new version is issued during the study). Pinnacle 21 Community Validator Version 4.0.0 (or higher if a new version is issued during the study) will be utilized to ensure compliance with CDISC standards.

Note that for PK and PD analysis, the 7th day of dosing of each treatment condition (dotinurad monotherapy, coadministration of dotinurad and allopurinol, and allopurinol monotherapy) will be the primary time point of interest for drawing conclusions regarding dose-response and DDI.

12.3. Analysis Populations

Several populations will be identified for purposes of analysis. As this is a Phase 1b dose-finding study in which both a description of the dose-response of monotherapy dotinurad AND DDI are primary objectives, the analysis populations will be based on each objective.

- Screened Population: All subjects signing informed consent.
- Safety Population: All subjects treated with at least one dose of dotinurad
- Primary Objective 1:
  - Dotinurad PK Population (dotinurad dose-response): All subjects with at least 80% compliance with dosing during Period 1 and with derivable PK parameters Cmax and AUC(0-24).
  - Dotinurad PD Population (dotinurad dose-response): All subjects with at least 80% compliance with dosing during Period 1 and with derivable PD parameters.
- Primary Objective 2:
  - DDI PK Population: All subjects with 80% compliance during each of the 3 treatment periods and with derivable PK parameters Cmax and AUC(0-24) for each of the 3 treatment periods.
  - DDI PD Population: All subjects with 80% compliance during each of the 3 treatment periods and with derivable PD parameters for each of the 3 treatment periods.

12.4. Handling of Missing Data

Missing data will not be replaced.

12.5. Baseline Characteristics

Baseline characteristics will be tabulated descriptively (eg, number and percent of subjects for each category for categorical parameters, and the number, mean, standard deviation, and range for continuous parameters).

12.6. Subject Disposition

Subject completion status and reasons for early termination will be tabulated descriptively.

12.7. Pharmacokinetics

The following PK parameters (Table 12)will be determined where possible from the plasma and urine concentrations of dotinurad, as well as for allopurinol and oxypurinol using noncompartmental methods in validated software program.

Table 12: PK Profile: Period 1 Day 1 and Day 4 and Day 7, Period 2 Day 14, and Period 3 Day 21 (Study UR1-DOT-103)

Parameter	Units[a]	Definition
$AUC_{0\text{-last}}$	h*ng/mL	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration, calculated using linear-up log-down trapezoidal summation
$AUC_{0\text{-}\tau}$	h*ng/mL	inter-dose interval area under the concentration-time curve from time 0 to the time of next dose, calculated using linear-up log-down trapezoidal summation
$AUC_{0\text{-inf}}$	h*ng/mL	area under the concentration-time curve from time 0 to infinity[b] (profile day 1 only)
$\%AUC_{extrap}$	%	percentage of area under the concentration-time curve due to extrapolation from the last quantifiable concentration to infinity (profile day 1 only)
C_{max}	ng/mL	maximum observed concentration
t_{max}	h	time to maximum observed concentration
t_{last}	h	time of the last quantifiable concentration
k_e	1/h	apparent terminal elimination rate constant, calculated by linear regression of the terminal linear portion of the log concentration versus time curve
$t_{1/2}$	h	apparent terminal elimination half-life
CL/F	L/h	apparent total clearance
Vz/F	L	apparent volume of distribution during the terminal phase
$R_{AUC0\text{-}\tau}$		accumulation ratio based on $AUC_{0\text{-}\tau}$
R_{Cmax}		accumulation ratio based on C_{max} during the dosing interval

$DAUC_{0\text{-last}}$	h*ng/mL/mg	dose normalized area under the concentration-time curve from time 0 to the time of the last quantifiable concentration, calculated using linear-up log-down trapezoidal summation[c]
$DAUC_{0\text{-}\tau}$	h*ng/mL/mg	dose normalized inter-dose interval area under the concentration-time curve from time 0 to the time of next dose, calculated using linear-up log-down trapezoidal summation[c]
$DAUC_{0\text{-inf}}$	h*ng/mL/mg	dose normalized area under the concentration-time curve from time 0 to infinity[bc] (profile day 1 only)
DC_{max}	ng/mL/mg	dose normalized maximum observed concentration[c]
$Ae_{t1\text{-}t2}$	mg	amount of the dose administered recovered over the time interval t1 to t2
$fe_{t1\text{-}t2}$	%	percentage of the dose administered recovered over the time interval t1 to t2
CL_R	L/h	renal clearance

The dosing interval τ is 24 hours.
[a] Units are based on concentration units (provided by the bioanalytical lab or preferred units for presentation of PK parameters) and dose units used in the study.
[b] Based on the last observed quantifiable concentration
[c] Calculated by dividing the parameter by the dose administered (mg)

Additional PK parameters may be determined where appropriate.

Pharmacokinetic analysis will be carried out where possible using actual dose administered (mg) and actual postdose blood sampling times. If an actual time is missing, the sample concentration result will be treated as missing unless there is scientific justification to include the result using the nominal time.

The parameters C_{max}, t_{last}, and t_{max} will be obtained directly from the concentration-time profiles. If C_{max} occurs at more than 1 timepoint, t_{max} will be assigned to the first occurrence of C_{max}.

The accumulation ratio(s) ($R_{AUC0\text{-}\tau}$ and R_{Cmax}) will be calculated as follows:

- $R_{AUC0\text{-}\tau}$ = $AUC_{0\text{-}\tau}$ Profile Day 4 / $AUC_{0\text{-}\tau}$ Profile Day 1
- R_{Cmax} = C_{max} Profile Day 4 / C_{max} Profile Day 1

Dotinurad steady state will be assessed via Helmert Contrasts, using trough concentrations within Period 1 only.

Other details regarding the PK analysis will be provided in the statistical analysis plan (SAP).

For the assessment of DDI, assessment of the geometric ratio of key PK parameters (Cmax, AUC) will be performed to determine the differences (if any) between monotherapy vs combination therapy of each drug, with tests of bioequivalence (BE) performed accordingly vis assessment of the point estimates and 90% CIs vs (80%, 125%) confidence bounds for BE.

12.8. Pharmacodynamics

The following pharmacodynamic (PD) parameters will be determined where possible from the serum and urine concentrations of absolute uric acid and baseline-adjusted uric acid using noncompartmental methods in validated software program.

Table 13: Pharmacodynamic Profile Screening Day -1 (Urine Only) and Period Days 1, 4, and 7, Period 2 Day 14, and Period 3 Day 21 (Serum and Urine) (Study UR1-DOT-103)

Parameter	Units	Definition
AUEC0-24	h*mg/dL	area under the effect-time curve from time 0 to 24 hours postdose[b]
Emax	mg/dL	maximum observed response
TEmax	h	time of maximum observed response
Aet1-t2	mg	amount excreted in urine over the time interval t1 to t2
CLR	mL/min	renal clearance

Comparison of the PD parameters between monotherapy and coadministration will be performed.

Response thresholds of serum uric acid levels will be determined using pre-dose concentrations on Days 7, 14, and 21, using <6 mg/dL, <5 mg/dL, and <4 mg/dL as prospectively defined response definitions. Dose proportionality and dose response (eg, on PD endpoints, vis-à-vis the number (%) of patients responding on serum uric acid by various response definitions) between the two dotinurad dose levels will be performed.

Other details regarding the PK analysis will be provided in the SAP.

12.9. Efficacy Analyses

Efficacy is assessed via the pharmacodynamic endpoints. There are no other efficacy assessment in this study.

12.10. Safety

The safety analysis will be descriptive in nature. All safety data will be listed, and data will be tabulated where the data warrant.

12.10.1. Adverse Events

Adverse events will be coded using the MedDRA coding dictionary; subject incidence of each system organ class and unique term will be tabulated. AE incidence will also be tabulated according to relationship to study medication and severity. Serious AEs and AEs resulting in premature discontinuation will be tabulated.

Adverse events starting after the first dose of treatment will be considered treatment-emergent adverse events and will be reported as occurring during the treatment phase and will be associated with the most recent treatment given. Any events reported after colchicine pre-treatment has begun will be reported as pre-treatment-emergent events associated with the colchicine treatment given.

12.10.2. Prior and Concomitant Medications

Prior and concomitant medications will be reviewed and coded using the WHO Drug Dictionary, and tabulated by treatment. Concomitant medications will be reported in a fashion similar to that of AEs.

12.10.3. Clinical Laboratories

Clinical laboratory observed values and changes from pre-treatment to on-treatment time points may be tabulated for continuous parameters, as warranted.

12.10.4. Vital Signs

Vital sign parameter outcomes will be assessed for clinical significance; observed values and changes from pre-treatment to on-treatment time points may be tabulated for continuous parameters, as warranted.

12.10.5. Physical Examination

Physical examination outcomes will be listed in data listings.

13. STUDY MONITORING, AUDITS, IRB, AND QUALITY

13.1. Study Monitoring

Before an investigational site can enter a subject into the study, a Sponsor representative will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor (or its delegate) and the investigator.

During the study, a monitor or Sponsor representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRF, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the eCRF with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original (or faxed/copied, if requested) records for each subject (e.g. clinic charts) which may include access to medical records for purposes of remote (i.e. not on-site at the Investigator's clinic) source data verification
- Record and report any protocol deviations not previously sent to the Sponsor (or its delegate)
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to Sponsor (or its delegate) and those SAEs that met criteria for reporting have been forwarded to the IRB

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

13.2. Audits and Inspections

Authorized representatives of the Sponsor, its delegate, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accuric acidly reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The

investigator should contact the Sponsor or its delegate immediately if contacted by a regulatory agency about an inspection.

13.3. Institutional Review Board/ Independent Ethics Committee

The Investigator must obtain appropriate IRB approval prior to study initiation. A copy of the written approval from the IRB and a copy of the approved ICF should be sent to the Sponsor or its delegate. It is also necessary to submit a list of the IRB members (including their Institution affiliations, gender makeup, and occupations) or supply a statement from the IRB specifying that the membership comply with applicable regulations.

The study protocol, subject information and consent form, the Investigator Brochure, available safety information, subject recruitment procedures (e.g., advertisements), information about payments and compensation available to the subjects and documentation evidencing the Investigator's qualifications should be submitted to the IRB/Ethics Committee for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

13.4. Quality Control and Quality Assurance

The investigator is responsible for all quality control and quality assurance for the performance of the study.

14. ETHICS

14.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The investigator must submit written approval to the Sponsor or its delegate before he or she can enroll any subject into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor or its delegate will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

14.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements and the Sponsor or its delegate's policy on Bioethics.

14.3. Written Informed Consent

The Investigator(s) will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated ICF and assent if applicable must be obtained before conducting any study procedures.

The Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

15. DATA HANDLING AND RECORDKEEPING

15.1. Inspection of Records

The Sponsor or its delegate will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

15.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for the Sponsor, its delegate, or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

15.3. Data Capture and Processing

Data will be captured on source documents and will be entered into an electronic data capture system via electronic case report forms (eCRFs) and will be processed according to a data management plan. The database will be cleaned and 'locked' according to that data management plan prior to the final statistical analysis being performed.

eCRFs will be completed for each study subject. It is the investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data entered in each subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, adverse events, and subject status.

The investigator, or designated representative, should complete the eCRF as soon as possible after information is collected. Any outstanding entries must be entered immediately after the final examination. An explanation should be given for all missing data.

16. PUBLICATION POLICY

All information concerning the product, as well as any matter concerning the operation of the Sponsor or its delegate, such as clinical indications for the drug, its formula, methods of manufacture, and other scientific data relating to it, that have been provided by the Sponsor or its delegate and are unpublished, are confidential and must remain the sole property of the Sponsor or its delegate. The Investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from the Sponsor or its delegate is obtained. The Sponsor has full ownership of the eCRFs completed as part of the study.

All publications and presentations of the results of the Study are governed by the applicable provisions of the Clinical Trial Agreement between the Sponsor (or its delegate) and the institution. By signing the study protocol, the investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals by the Sponsor or its delegate. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement. The Investigator may not publish or present any information on this study without the express written approval of the Sponsor or its delegate. Additionally, the Sponsor or its delegate may, for any reason, withhold approval for publication or presentation. Such manuscript or materials should be provided for Sponsor/delegate review only after the final database, which has been approved by Quality Assurance, is available.

17. LIST OF REFERENCES

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