The Impact of Initiating Dotinurad Urate-Lowering Therapy at Different Time Windows on Gout Flare Resolution Time: A Multicenter, Randomized, Parallel-Controlled Study

PART I – INFORMATION

You are being invited to take part in a research study that will be conducted at the Department of Rheumatology & Immunology, The First Affiliated Hospital of Wenzhou Medical University, and other participating centers. Before you decide whether to participate, please read this document carefully. It explains why the study is being done, what will happen to you, and the possible benefits, risks, and inconveniences. You may discuss it with your family, friends, or personal physician. If anything is unclear, please ask the study doctor for clarification.

1. Why is this study being performed?

Gout is a crystal-induced arthritis caused by deposition of monosodium urate (MSU) and is directly related to hyperuricemia. The prevalence of gout in Chinese adults is approximately 3.2 %, and the age-standardized rate continues to rise by ~0.9 % per year, often affecting younger individuals and imposing a heavy socioeconomic burden.

Persistent reduction of serum uric acid (sUA) is the key to preventing flares, tophi, bone destruction, and excess mortality, and to improving quality of life. However, international guidelines differ on when to start urate-lowering therapy (ULT). Some (e.g., the 2019 Chinese Guidelines for the Diagnosis and Treatment of Hyperuricemia and Gout) recommend waiting 2–4 weeks after an acute flare has resolved, whereas others (e.g., the 2020 American College of Rheumatology Guideline for the Management of Gout) allow ULT initiation during an acute attack provided effective anti-inflammatory prophylaxis is given.

Recent randomized trials show that early ULT does not prolong flare duration, increase pain scores, or raise relapse rates, and may improve long-term adherence. Dotinurad is a newly marketed selective urate reabsorption inhibitor (SURI) with potent urate-lowering efficacy, but no published data exist on its use initiated during an acute flares.

This study will evaluate whether initial dotinurad during an acute gout flare prolongs the time to flare resolution.

2. Who can take part?

You may be eligible if ALL of the following apply:

- Male or female individuals aged 18-70 years old.

- Meet the 2015 ACR/EULAR diagnostic criteria of gout.

- With an onset of acute gout flares within 7 days.

- With gout experiencing gout flares ≥2 times; or with gout experiencing gout flares 1 time and is younger than 40 years old; or with gout experiencing gout flares 1 time and has a serum uric acid level greater than 480 μmol/L and/or has co-morbidities (renal function impairment, hypertension).

- Able to give written informed consent before any study procedure.

You CANNOT take part if ANY of the following apply:

- Has secondary hyperuricemia.

- Serum uric acid level < 360 μmol/L.

- Used IL-1β inhibitors within 6 months before screening.

- Used uric acid-lowering drugs within 1 month before screening.

- Used anti-inflammatory drugs within 14 days before screening.

- Comorbidities with nephrolithiasis or clinical urinary calculi

- History of kidney transplantation or dialysis.

- Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2.

- AST or ALT > 2 times the upper limit of normal.

- Systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 100 mmHg during the screening period.

- White blood cell count < 3.5 × 10^9/L, or platelet count < 100 × 10^9/L, or hemoglobin < 90 g/L.

- Currently in the treatment period of malignant tumors, or within 6 months after the end of the treatment period.

- Congestive heart failure (New York Heart Association [NYHA] cardiac function classification II-IV), confirmed ischemic heart disease, peripheral artery disease and/or cerebrovascular disease (including patients who have recently undergone coronary artery bypass grafting or angioplasty)

- Hypersensitivity to the study drugs or their excipients, or all of urine alkalinizer (potassium citrate/sodium citrate hydrate compound preparations).

- Have active gastrointestinal ulcers/bleeding, or have had a recurrence of ulcers/bleeding in the past.

3. What will happen if I take part?

If you agree, you will:

- Discuss the study with your doctor and sign this consent.

- Undergo screening assessments: vital signs, physical examination, height/weight, ECG, laboratory tests (blood/urine, liver/kidney function, ESR, CRP), renal ultrasound/X-ray, and gout-pain scoring.

If eligible you will be randomly assigned (1:1) to:

- Treatment group: dotinurad 2 mg once daily + colchicine 1 mg once daily + etoricoxib （120 mg days 1–3 then 60 mg days 4–7）, 4 weeks, or

- Control group: colchicine 1 mg once daily + etoricoxib （120 mg days 1–3 then 60 mg days 4–7）, 2 weeks. Then, dotinurad 2 mg once daily + colchicine 1 mg once daily, 2 weeks.

You have a 50 % chance of being assigned to the control group. Your assignment is completely random—like flipping a coin—and even your study doctor cannot choose or change it. Whichever group you are placed in, you will receive the same careful medical attention and advice.

During the study you not take any other medicines that treat gout or could influence the results. If, after your first flare has settled, you suffer another attack that becomes unbearable, you may take “rescue” medicines such as other NSAIDs or corticosteroids and must record exactly what you took in your diary card.

You will attend every follow-up visit requested by the doctor, undergo the required tests, and tell the doctor how you feel after each dose. The doctor will record how quickly your symptoms improve, whether you have any new flares, and how many occur. Please report any discomfort or problems to your study doctor immediately.

Please complete the following procedures under the supervision of the study doctor and in accordance with the study protocol.

Visit 3 will be conducted by video call; all other visits should be done on-site unless your doctor instructs otherwise.

Schedule of assessments

- Visit 1(Screening)

- Visit 2 (dosing day)

- Visit 3 (day 3)

- Visit 4 (day 7)

- Visit 5 (day 14)

- Visit 6 (day 28)

4. Are there alternative treatments?

Yes. You may decline to participate and instead receive standard care with any available urate-lowering drug (allopurinol, febuxostat, benzbromarone) and/or anti-inflammatory agents (NSAIDs, corticosteroids, colchicine) at any time. Refusal to enter or later withdrawal will not affect your routine medical care.

5. What are the possible benefits?

- Your acute flare may resolve and future flares may be fewer.

- Your sUA may be better controlled.

- Information gained may help other patients in the future.

Benefit cannot be guaranteed; individual responses vary.

6. What are the possible risks?

Every medicine can cause side-effects, and the study drugs are no exception.

Dotinurad tablets – adverse reactions

Very common (≥ 10 %): gouty arthritis.

Common (≥ 1 % – < 10 %): gout flare, arthritis, limb discomfort, kidney stone, alanine aminotransferase increased, alpha-one-microglobulin increased, blood uric acid decreased, urine beta-two-microglobulin increased, gamma-glutamyl transferase increased..

Uncommon (≥ 0.1 % – < 1 %): high triglyceride blood level, high lipid blood level, low uric acid blood level, high cholesterol blood level, high glucose blood level, high phosphate blood level, high blood pressure, loose stool, liver fat deposition, liver injury, itching, joint pain, back pain, limb pain, inflammation around the joint, trace albumin in urine, blood in urine, calcium deposits in kidney, kidney cyst, kidney function damage, benign prostate enlargement, blood creatinine increased, low-density lipoprotein increased, aspartate aminotransferase increased, high-density lipoprotein decreased, beta-two-microglobulin in urine increased, hidden blood in urine positive, albumin detected in urine, amylase increased, blood creatine phosphokinase increased, protein detected in urine, urine albumin-to-creatinine ratio increased, white blood cell count decreased, beta-N-acetyl-D-glucosaminidase in urine increased, diastolic blood pressure increased, eosinophil count increased, neutrophil count decreased..

Colchicine – adverse reactions

Gastro-intestinal: belly pain, loose stool, vomiting and poor appetite are common early unwanted effects and may occur in up to eighty out of every one hundred people; severe cases can lead to body-water loss and salt imbalance. Long-term use may cause serious bleeding gut inflammation or poor food absorption.

Muscle and nerve: weakness of muscles near the body trunk and/or blood creatine phosphokinase increase; damage to muscle cells can occur together with long-fibre nerve damage that causes numbness, prickling and weakness. This muscle-nerve damage is rare and usually appears in people who take the drug for long periods to prevent gout and who have mild kidney function reduction; it can lead to life-threatening failure of blood-cell production.

Bone-marrow suppression: platelet count drop, neutrophil count drop, even complete failure of blood-cell production.

Shock: low urine output, blood in urine, fits and loss of awareness.

Harm to the unborn child.

Others: hair loss, skin rash, fever and liver damage.

Meloxicam – adverse reactions

Abnormalities of the blood and lymphatic system: thrombocytopenia; Immune system abnormalities: Allergic reactions, including allergic or anaphylactic reactions such as shock; Metabolic and nutritional disorders: Hyperkalemia; Mental disorders: insomnia, confusion, hallucinations, restlessness and unease; Neurological abnormalities: Taste disorders; Abnormalities in breathing, chest and mediastinum: bronchospasm; Gastrointestinal abnormalities: abdominal pain, oral ulcers, peptic ulcers including perforation and bleeding (mainly occurring in elderly patients); Abnormalities of the liver and gallbladder: hepatitis, jaundice, liver failure; Abnormalities of the skin and subcutaneous tissue: angioedema, pruritus, erythema, Stevens-Johnson syndrome, toxic epidermal necrolysis, rubella, fixed drug eruption; Abnormalities of the kidneys and urinary system: Renal insufficiency, including renal failure.

If you experience any discomfort, new symptoms, or unexpected events—whether or not you think they are related to the study drugs—contact your study doctor immediately. The doctor will assess the problem and give appropriate care.

7. Confidentiality

All data will be coded; your identity will not be disclosed outside the study team except for medical emergencies or legal requirements. Regulatory authorities and the Ethics Committee may inspect original records while maintaining confidentiality.

8. Costs & compensation

If you take part in this study, you will not have to pay for the drug dotinurad tablets. All tests that are performed are part of the usual care that the study doctor considers necessary for your condition and are not provided free of charge. Likewise, any standard treatment or tests you may need for other illnesses that you have at the same time will not be covered by the study.

You will be asked to attend a total of 6 visits. After you have completed every visit required by the study plan, you will receive a transportation allowance of RMB 400.

9. Injury compensation

The sponsor has purchased clinical-trial insurance. If you suffer injury directly related

to study participation, the hospital and sponsor will provide free treatment and legal compensation, except for injuries due to your underlying disease or non-compliance.

10. Voluntary participation & withdrawal

Participation is entirely voluntary. You may refuse to enter or withdraw at any time without penalty or loss of medical benefit. The investigator may withdraw you if continuation is judged unsafe or if you fail to comply with study requirements.

11. Contacts

For study questions: __Yongji Li___ Mobile _____.

For subject-rights questions: Ethics Committee, The First Affiliated Hospital of Wenzhou Medical University, Tel +86 577 5557 8027.

PART II – INFORMED CONSENT SIGNATURE

1. Subject (or legally authorised representative) statement

I have read (or had read to me) the above information. I have had the opportunity to ask questions and have received satisfactory answers. I understand the aims, procedures, possible benefits and risks of this study and consent to participate voluntarily.

Subject name _____

Subject signature _____

Date ___/___/____ Tel _____

Legal representative (if applicable) name _____

Signature _____

Relationship to subject _____

Date ___/___/____ Tel _____

Impartial witness (if required) name _____

Signature _____

Date ___/___/____ Tel _____

2. Investigator statement

I have explained the study to the subject and answered all questions. I believe that the subject has understood the information and gives consent freely.

Investigator name _____

Version Number：1.0 Version Date: May 26, 2026

Signature _____

Date ___/___/_____ Tel _____