Informed Consent Form

Protocol Title: Efficacy and Safety of Etrasimod Versus Mesalazine in Chinese Adult Patients with Active Ulcerative Colitis: A Multicenter, Randomized, Open-Label, Superiority Trial

Version: V1.0

Version Date: June 6, 2026

Dear Subject:

We invite you to participate in the study "Efficacy and Safety of Etrasimod Versus Mesalazine in Chinese Adult Patients with Active Ulcerative Colitis: A Multicenter, Randomized, Open-Label, Superiority Trial", which has been reviewed and approved by the Ethics Committee of Sir Run Run Shaw Hospital, Zhejiang University School of Medicine.

This informed consent form provides you with information to help you decide whether to participate in this clinical study. Your participation in this study is entirely voluntary, and your decision will not affect your rights to normal medical care and treatment at our hospital. If you choose to participate in this study, our study team will do its best to protect your safety and rights throughout the study.

Please read this form carefully. If you have any questions, please ask the investigator responsible for this study.

I. Background and Objectives

1.1 Background

Ulcerative colitis (UC) is a relapsing, chronic inflammatory bowel disease of unknown etiology that mostly involves the colorectum. The clinical manifestations of UC patients include persistent/recurrent diarrhea, mucous bloody stools, abdominal pain, and tenesmus, accompanied by a high incidence of extraintestinal manifestations, which seriously affect quality of life. The prevalence of UC is on the rise; the incidence of UC in China reached as high as 8.95 per 100,000 person-years in 2016, and the global number of UC patients was estimated at 5 million in 2023, representing a severe situation.

UC currently cannot be completely cured. The goals of treatment are to induce clinical remission, achieve mucosal healing, improve quality of life, and prevent complications, thereby ultimately improving long-term outcomes. Pharmacotherapy is currently the mainstay of UC treatment, usually including mesalazine (5-aminosalicylic acid, 5-ASA), glucocorticoids, and immunomodulators, as well as biologics and small-molecule drugs.

Etrasimod is a novel S1P receptor modulator that can specifically target S1P receptors 1/4/5, preventing the egress of T lymphocytes from secondary lymphoid organs and attenuating the differentiation of T helper 1/T helper 17 cells, thereby alleviating UC inflammation and slowing the occurrence and progression of UC.

As a conventional first-line treatment for UC, mesalazine has obvious limitations, including inadequate response in some patients and a risk of renal impairment. In contrast, etrasimod has demonstrated favorable efficacy and safety in the treatment of UC. However, data comparing the efficacy and safety of etrasimod versus mesalazine are currently lacking. This study aims to explore the differences in efficacy and safety between etrasimod and the conventional mesalazine regimen, thereby providing empirical evidence for optimizing clinical treatment strategies for UC.

1.2 Objective

This study aims to evaluate the efficacy and safety of etrasimod versus mesalazine in the treatment of active UC.

2. Study Process

2.1 Study Overview

This study is a randomized controlled, multicenter, clinical interventional study. It is planned to enroll a total of 320 subjects, and the expected number of subjects participating at this center is 50.

If you agree to participate in this study, you will need to sign this informed consent form. Afterwards, we will assess you against the inclusion and exclusion criteria. If you meet the inclusion criteria and do not meet the exclusion criteria, you will be enrolled in this study and will have a 1/2 chance of entering the experimental group (etrasimod treatment group) and a 1/2 chance of entering the control group (mesalazine treatment group). Which group you ultimately enter depends on the result of computer-based randomization, and neither you nor your doctor has the right to interfere with the allocation result. Therefore, if you decline either of the above two treatment regimens, you may choose not to participate in or to withdraw from this study and discuss other treatment options with your doctor again.

2.2 Intervention Regimens

If you are assigned to the experimental group, the treatment regimen you will receive is: etrasimod tablets (2 mg/tablet), orally, one tablet daily, for 24 weeks of treatment.

If you are assigned to the control group, the treatment regimen you will receive is: mesalazine enteric-coated tablets (0.5 g/tablet), orally, with the specific daily dose determined by the investigator according to your condition, for 24 weeks of treatment.

The use of etrasimod in this study is off-label (beyond the approved indications). According to its label, etrasimod is approved for adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, loss of response, or intolerance to conventional therapy or biologics. In this study, however, etrasimod is used in newly diagnosed patients with active ulcerative colitis and in patients with mildly to moderately active ulcerative colitis, which constitutes off-label use.

2.3 Visit Contents

The follow-up contents and examination/assessment items involved in this study mainly include the following aspects:

1) Demographic data (V1 visit): including date of birth, sex, ethnicity, place of residence, marital status, occupation, education level, income level, and type of medical insurance. 2) Physical examination (V1, V2, V3, V4 visits): including height (cm) and weight (kg).

3) Vital signs (V1, V2, V3, V4 visits): including blood pressure (systolic/diastolic), body temperature, respiratory rate, and heart rate.

4) Electrocardiogram (V1 visit).

5) Laboratory tests (V1, V2, V3, V4 visits): including complete blood count and blood biochemistry (including liver and renal function).

6) Pregnancy test (V1 visit): females only.

7) Fundus examination (V3 visit): the investigator will assess whether to perform it according to the study protocol.

8) Medical history (including UC history) (V1, V2, V3, V4 visits): including disease name, date of diagnosis, disease location, disease severity, concomitant treatment measures taken, etc., as well as participation in other clinical studies, allergy history, and vaccination history (including vaccine names, vaccination dates, etc.).

9) Medication history (including UC medication history) (V1, V2, V3, V4 visits): including the generic names, doses, start dates, stop dates, or continued use of medications used in the past 3 months.

10) UC concomitant and accompanying medications (V1, V2, V3, V4 visits): the generic name, start date, dosing regimen, date of and reason for discontinuation, duration of use, and indication of each medication.

11) Inflammatory marker tests (V1, V2, V3, V4 visits): including fecal calprotectin (FCP) and C-reactive protein (CRP).

12) Endoscopy (including proctosigmoidoscopy) (V1, V3, V4 visits).

13) Histological biopsy (V1, V3, V4 visits).

14) Intestinal ultrasound examination (V1, V2, V3, V4 visits).

15) Health-related quality of life assessment (IBDQ scale) (V1, V2, V3, V4 visits).

16) Partial modified Mayo score, including stool frequency and rectal bleeding (V1, V2, V3, V4 visits).

17) Adverse event monitoring (V1, V2, V3, V4 visits).

[Note: The V1 visit is at baseline Week 0, the V2 visit is at Week 6±2 weeks, the V3 visit is at Week 12±2 weeks, and the V4 visit is at Week 24±4 weeks].

3. Possible Risks and Corresponding Measures

The investigational drugs involved in this study include etrasimod and mesalazine; their adverse events (AEs) and management measures are as follows.

3.1 Etrasimod-Related Adverse Events and Management

In patients receiving etrasimod for the treatment of ulcerative colitis, common adverse reactions include headache, elevated liver function test values, dizziness, arthralgia, and hypertension. The vast majority of these adverse reactions are mild to moderate and can be controlled with or without medical intervention.

During etrasimod treatment, the following categories of adverse reactions require special attention: Hepatic abnormalities: etrasimod can cause transaminase elevations; liver function should be monitored regularly during treatment, and in rare cases significant liver injury may occur. Bradycardia and atrioventricular conduction delay: after initiation of etrasimod, transient heart rate slowing and atrioventricular conduction delay may occur, usually within a few hours after the first dose; most cases are asymptomatic and resolve spontaneously. Infection: by reversibly blocking lymphocyte egress from lymphoid organs, etrasimod may increase the risk of infection; common infections are upper respiratory tract infections and urinary tract infections, mostly mild to moderate. Macular edema: S1P receptor modulators may increase the risk of macular edema, with higher risk in patients with diabetes, uveitis, and/or a history of underlying retinal disease. Elevated blood pressure: systolic and diastolic blood pressure may increase slightly during etrasimod treatment. Most of the above adverse reactions are mild and manageable; a few are serious adverse events requiring timely management.

Management measures for etrasimod-related adverse reactions: ① Hepatic abnormalities: transaminase and bilirubin levels within the past 6 months should be obtained before treatment, and regular monitoring is required during treatment (periodic testing is recommended after treatment initiation). If transaminases are significantly elevated (more than 3 times the upper limit of normal) accompanied by a marked increase in total bilirubin (more than 2 times the upper limit

of normal), the drug should be suspended and hepatoprotective treatment given. ② Bradycardia and atrioventricular conduction delay: an electrocardiogram should be performed before treatment to evaluate cardiac status. For high-risk patients with a resting heart rate <50 beats/min, a history of second-degree Mobitz type I atrioventricular block, myocardial infarction, or heart failure, heart rate monitoring for at least 4 hours should be performed after the first dose; if symptoms such as dizziness, fatigue, or chest tightness occur, the physician should be informed promptly. ③ Infection: a complete blood count (including lymphocyte count) should be obtained before treatment; treatment initiation should be delayed if an active infection is present. When signs of infection such as fever, sore throat, or cough occur during treatment, the physician will assess the severity and, if necessary, suspend the drug and provide anti-infective treatment. If the peripheral blood lymphocyte count falls below 0.2×10^9/L and is confirmed on repeat testing, treatment should be interrupted until recovery to above 0.5×10^9/L before restarting. ④ Macular edema: for patients with diabetes, uveitis, and/or a history of underlying retinal disease, regular ophthalmologic examinations are recommended before starting treatment and during treatment; if blurred vision or metamorphopsia occurs, it should be reported immediately and a fundus examination (including the macula) arranged; once macular edema is diagnosed, the drug should be suspended and appropriate treatment given. ⑤ Elevated blood pressure: blood pressure is monitored regularly during treatment, and any elevation can be managed promptly. ⑥ Common discomforts such as headache and nausea: these are mostly mild and can be managed symptomatically or observed.

3.2 Mesalazine-Related Adverse Events and Management

In patients receiving mesalazine for the treatment of ulcerative colitis, common adverse reactions include diarrhea, nausea, abdominal pain, headache, vomiting, and rash. The vast majority of these adverse reactions are mild to moderate and can be controlled with or without medical intervention.

During mesalazine treatment, the following categories of adverse reactions require special attention: Renal impairment: mesalazine is rapidly excreted by the kidneys in the form of metabolites and may cause acute/chronic interstitial nephritis, nephrotic syndrome, and renal insufficiency; most cases are reversible after discontinuation, but some cases of interstitial nephritis carry a risk of irreversibility. Hepatic abnormalities: a small number of patients may develop transaminase elevation, hepatitis, cholestatic hepatitis, or even liver failure. Hematologic abnormalities: rare but serious changes in blood cell counts include aplastic anemia, agranulocytosis, pancytopenia, and thrombocytopenia. Cardiotoxicity: rare myocarditis, pericarditis, and pericardial effusion. Pulmonary reactions: a small number of patients may

develop allergic and fibrotic pulmonary reactions, including dyspnea, cough, allergic alveolitis, and interstitial lung disease. Acute intolerance syndrome: some patients may experience acute intolerance reactions such as cramps, acute abdominal pain, fever, severe headache, and rash, requiring immediate discontinuation. Pancreatitis: a small number of patients may develop elevated amylase and acute pancreatitis. Most of the above serious adverse reactions resolve after discontinuation, but a few may be life-threatening and require timely management.

Management measures for mesalazine-related adverse reactions: ① Renal impairment: renal function and urinalysis should be checked regularly before and during treatment; if signs of renal function deterioration appear, mesalazine-induced nephrotoxicity should be considered, the drug should be suspended, and a nephrology consultation requested. ② Hepatic abnormalities: liver function parameters (ALT, AST, etc.) are monitored regularly during treatment; if transaminases are significantly elevated or signs of hepatotoxicity appear, the drug should be suspended and hepatoprotective treatment given. ③ Hematologic abnormalities: complete blood counts are rechecked regularly; if significant leukopenia, thrombocytopenia, or signs of aplastic anemia appear, the drug should be suspended and a hematology consultation requested. ④ Cardiotoxicity (e.g., myocarditis, pericarditis): if symptoms related to pericarditis/myocarditis such as chest pain, shortness of breath, or fever occur, the drug should be discontinued immediately and a cardiology consultation requested. ⑤ Pulmonary reactions: if respiratory symptoms such as dyspnea or cough occur, assess whether they are drug-related; discontinue the drug if necessary and perform chest imaging and pulmonary function tests. ⑥ Pancreatitis: if persistent upper abdominal pain, nausea, or vomiting occurs, serum amylase/lipase should be tested; once diagnosed, discontinue the drug immediately and treat according to standard pancreatitis management. ⑦ Acute intolerance syndrome: if symptoms such as cramps, acute abdominal pain, fever, severe headache, or rash occur, treatment must be stopped immediately. ⑧ Rash and allergic reactions: mild rash can be treated with oral antiallergic agents; severe cases (e.g., Stevens-Johnson syndrome, DRESS syndrome) require immediate discontinuation and systemic glucocorticoid therapy. ⑨ Common discomforts such as headache, nausea, and diarrhea: these are mostly mild and can be managed symptomatically or observed; they resolve within 24-48 hours after discontinuation.

In addition to the above situations, if any other discomfort occurs, please inform the study physician at any time. The physician will take measures such as suspension, dose reduction, discontinuation, symptomatic treatment, or specialist consultation according to severity, and will document the entire process.

4. Expected Benefits

Etrasimod is a novel oral drug that has been shown in clinical studies to have favorable efficacy for UC. This study aims to compare the efficacy of etrasimod with that of mesalazine. If the results of this study confirm that etrasimod (the study drug) is superior to mesalazine (a routinely used clinical drug) and you are assigned to the etrasimod treatment group, you may obtain better treatment outcomes. Of course, you may also not benefit directly from this study. However, the data you provide will help the investigators further clarify the efficacy and safety of etrasimod in Chinese UC patients, thereby exploring better early treatment strategies, which may ultimately benefit your future medical care as well as other patients with the same disease.

5. Alternative Treatments

In addition to the treatment regimens involved in this study, the following treatment regimens are also clinically available for this disease, including but not limited to: conventional therapeutic agents (e.g., mesalazine, glucocorticoids, and immunosuppressants), biologics (e.g., infliximab, vedolizumab, guselkumab, risankizumab, and mirikizumab), and small-molecule inhibitors (e.g., upadacitinib).

6. Study Costs

All examination and assessment items involved in this study are routine clinical examinations, and no additional examinations or procedures are added; therefore, participating in this study will not incur additional medical costs for you. The costs arising from these routine examinations shall be borne by you. In addition, this study provides the following subsidies:

1. Provision of study drug: if you are randomly assigned to the etrasimod treatment group, we will provide you with 1 bottle of the study drug per month (provided free of charge until your withdrawal/the end of the study). When collecting the medication, you need to return the empty bottle from the previous month to the investigator.

2. Additional subsidy: if you are randomly assigned to the mesalazine treatment group, we will provide you with an additional subsidy of RMB 300 per month. The subsidy will be paid in a lump sum after you complete your last visit. If you do not complete the visits required by the study protocol, the subsidy will be paid according to the number of visits you actually completed. The subsidy will be paid directly into your account or the account of your legal representative.

3. Transportation subsidy: to facilitate your travel to and from the study visits, we will provide you with a subsidy of RMB 100 per visit (follow-up). It will be paid in a lump sum after you complete your last visit. If you do not complete the visits required by the study protocol, the subsidy will be paid according to the number of visits you actually completed. The subsidy will be

paid directly into your account or the account of your legal representative.

7. Compensation and Management of Injury

If any harm occurs, we will provide you with timely treatment. If the investigator determines that the harm you experienced is related to this study, the study will bear the corresponding treatment costs and provide compensation/indemnification (clinical research insurance will be purchased for you).

8. Confidentiality

If you decide to participate in this study, your participation and your personal information and related data in the study will be kept confidential. Your study-related data will be identified by a study number rather than your name. Information that can identify you will not be disclosed to anyone outside the study team unless your permission is obtained. All study members and collaborators are required to keep your identity and related information confidential. Your records will be kept in a locked filing cabinet accessible only to study personnel. To ensure that the study is conducted in accordance with regulations, government authorities or members of the ethics review committee may, when necessary, review your personal data at the study site in accordance with regulations. When the results of this study are published, none of your personal data will be disclosed.

9. Voluntariness

You may choose not to participate in this study, or you may notify the investigator at any time to request withdrawal from the study; your data will not be included in the study results, and none of your medical treatment or rights will be affected as a result.

If you require other treatment, or if you do not comply with the study plan, or if you experience a study-related injury, or for any other reason, the study physician may terminate your continued participation in this study.

10. Subject Obligations

As a subject, you need to truthfully provide your medical history (including UC history, allergy history, vaccination history, etc.) and your current physical condition, and inform the study physician whether you have participated in or are currently participating in any other clinical study within the past 3 months. During this study, if any discomfort or adverse event occurs (including new symptoms, worsening of existing symptoms, or abnormal test results), you should inform the

study physician promptly. You must complete all scheduled follow-up visits and examination/assessment items on time as required by the study protocol, and comply with the following medication and related restrictions: during the study, the use of any UC treatment drugs outside this study—including other biologics, JAK inhibitors, and immunomodulators (such as azathioprine, 6-mercaptopurine, methotrexate, etc.)—is prohibited. For patients already using oral corticosteroids at baseline, continued use is permitted but mandatory tapering is required per the protocol (starting 2 weeks after enrollment, the dose is reduced by 5 mg every 1-2 weeks and must be completely discontinued within 10 weeks); those not using corticosteroids at baseline must not newly start them during the study. For patients already using mesalazine rectal topical preparations (suppositories, enemas, etc.) or traditional Chinese medicine enemas at baseline, continued use is permitted but the dose must not be increased; those not using them at baseline must not newly start them during the study. If you need to add any new medication during the study (including prescription drugs, over-the-counter drugs, dietary supplements, etc.), you must obtain the study physician's consent in advance. Because etrasimod may cause transient heart rate slowing, concomitant use with the following drugs should be avoided during treatment: antiarrhythmic drugs (especially Class Ia [e.g., quinidine, procainamide] and Class III [e.g., amiodarone, sotalol]), drugs that may prolong the QT interval, beta-blockers, calcium channel blockers, and other drugs that may affect heart rate; concomitant use with strong or moderate CYP enzyme inhibitors or inducers (e.g., fluconazole, rifampicin) should also be avoided. Etrasimod tablets should be swallowed whole with water and must not be split, crushed, or chewed; it is recommended to take the drug with food during the first 3 days to reduce the possible transient decrease in heart rate. Mesalazine should not be used concomitantly with lactulose or drugs that lower fecal pH, so as not to affect its efficacy; caution is required when used with anticoagulants (e.g., warfarin), which may increase the risk of bleeding; concomitant use with glucocorticoids may increase the risk of gastrointestinal bleeding; concomitant use with sulfonylurea oral hypoglycemic agents may enhance their hypoglycemic effect; concomitant use with methotrexate, azathioprine, or 6-mercaptopurine may increase the risk of myelosuppression; caution is required when used with antiplatelet drugs or nonsteroidal anti-inflammatory drugs (e.g., aspirin, ibuprofen), which may increase the risk of bleeding or renal impairment; if antacids (e.g., calcium carbonate D3 tablets, omeprazole) are needed during mesalazine treatment, they may affect the absorption of mesalazine, and it is recommended to take them at least 2 hours apart from other medications. If vaccination with a live attenuated vaccine is needed, it should be completed at least 4 weeks before starting etrasimod treatment; live attenuated vaccines must not be administered during the study or within 2 weeks after discontinuing etrasimod. If you are a woman of childbearing potential, you must use

effective contraception during the study and for at least 14 days after discontinuing the study drug; if you or your partner becomes pregnant during the study, you must inform the study physician immediately. If you decide to withdraw from this study, please notify your study physician in a timely manner; none of your medical treatment or rights will be affected as a result.

11. Contact Information

You may at any time obtain information and materials related to this study and learn about its progress. If you have any questions related to this study, or if you experience any discomfort or harm during the study, you may contact the study personnel at any time (Dr. Jing Liu, 18768116867, 15th Floor East, Inpatient Department of Gastroenterology, Qiantang Campus, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang Province).

If you have any questions about your rights as a subject participating in research, please contact the Ethics Committee of Sir Run Run Shaw Hospital, Zhejiang University School of Medicine (0571-86006811).

Informed Consent Form

Signature Page

I have read this informed consent form.

I have had the opportunity to ask questions, and all of my questions have been answered.

I understand that participation in this study is voluntary.

I may choose not to participate in this study, or I may withdraw at any time after notifying the investigator without being subject to discrimination or retaliation, and none of my medical treatment or rights will be affected as a result.

If I require other treatment, or if I do not comply with the study plan, or if I experience an injury related to this study, or for any other reason, the study physician may terminate my continued participation in this study.

I will receive a signed copy of this "Informed Consent Form".

Subject's name (print): _____ Subject's signature: _____

Contact information: _____Date: _____ (year) _____ (month) _____ (day)

If the subject is unable to read and sign the informed consent form due to reasons such as incapacity, or if the subject is a minor, the informed consent process shall be conducted by and the form signed by his/her guardian.

Guardian's name (print): _____ Guardian's signature: _____

Relationship to the subject: _____

Contact information: _____ Date: _____ (year) _____ (month) _____ (day)

If the subject is unable to read the informed consent form (e.g., an illiterate subject), the informed consent process shall be witnessed and signed by an impartial witness.

Witness's name (print): _____ Witness's signature: _____

Contact information: _____ Date: _____ (year) _____ (month) _____ (day)

I have accurately explained this document to the subject; he/she has accurately read this informed consent form, and I confirm that the subject had the opportunity to ask questions. I certify that he/she has consented voluntarily.

Investigator's name (print): _____Investigator's signature: _____

Contact information: _____ Date: _____ (year) _____ (month) _____ (day)