# Informed Consent Form for Scientific Research Project

**Project Title**:Efficacy and Safety Observation of a Novel Calcium Channel Modulator in the Treatment of Patients with Restless Legs Syndrome and Its Variant Types

**Sponsor**: Beijing Friendship Hospital Affiliated to Capital Medical University

**Research Institution**: Beijing Friendship Hospital Affiliated to Capital Medical University

**Principal Investigator of the Institution**: Tuo Houzhen

Dear Subject,

You are invited to participate in the research project titled *Efficacy and Safety Observation of a Novel Calcium Channel Modulator in the Treatment of Patients with Restless Legs Syndrome and Its Variant Types*. Please read this informed consent form carefully and make a prudent decision on whether to participate in this study. When your research doctor or researcher discusses the informed consent form with you, you may ask them to explain any unclear parts. We encourage you to fully discuss with your family and friends before deciding to participate in this study. If you are currently participating in other research projects, please inform your research doctor or researcher. The purpose, background, research procedures and other important information of this study are as follows:

## I. Research Background

The research background of this study is that Restless Legs Syndrome (RLS) is a common neurological sensorimotor disorder. Its core manifestation is intolerable discomfort (such as crawling sensation, burning sensation, pain, etc.) in the legs at rest in the evening or night, which can be relieved by movement. It seriously affects sleep, and may also cause depression and anxiety, reducing the quality of life. In addition to the legs, the discomfort may also involve the bladder, abdomen, chest, oral cavity and other parts. Such cases are called variant RLS, for which there is currently no unified treatment standard.

In clinical practice, typical RLS is commonly treated with dopaminergic drugs (e.g.,

pramipexole). However, some patients may experience diminished efficacy or adverse reactions such as nausea and impulse control disorders. Alternative medications such as gabapentin and pregabalin are associated with side effects like dizziness and drowsiness. Opioid drugs are only used for refractory cases due to the risk of addiction, resulting in significant limitations in treatment. The treatment of variant RLS is mostly based on that of typical RLS, relying on physicians' empirical medication, with uncertain efficacy and insufficient evidence support.

**Important Note**: Crisugabalin Besilate Capsules used in this study is a novel third-generation calcium channel modulator. Its currently approved indication is not RLS (including typical and variant types), and this treatment is an off-label use. By reducing the release of excitatory neurotransmitters, this drug has shown certain potential in the treatment of neuropathic pain, and theoretically may improve RLS symptoms. However, it should be clarified that the current clinical efficacy and safety data of this drug for RLS (especially variant RLS) are limited. In terms of efficacy, there is no sufficient large-sample research to confirm its improvement effect on RLS symptoms and the stability of long-term efficacy. In terms of safety, although it has high target selectivity, unknown adverse reactions may still occur after medication, and the tolerance varies among different patients. This study will systematically evaluate the efficacy and safety of this drug in the treatment of typical and variant RLS, providing reference for clinical practice.

## II. Research Purpose

The purpose of this study is to prospectively observe the improvement of symptoms in patients with RLS and its variant types after treatment with Crisugabalin Besilate Capsules (the drug has been approved for marketing by the National Medical Products Administration of China). It aims to objectively evaluate the efficacy and safety of this novel calcium channel modulator, and provide high-level evidence-based medical evidence for the individualized drug treatment of patients with RLS and its variant types.

## III. Research Procedures

**1.How many people will participate in this study?**

Approximately 20 people will participate in this study conducted at 1 medical institution, and about 20 people will participate in this study at Beijing Friendship Hospital Affiliated to Capital Medical University.

**2.Research Steps**

If you agree to participate in this study, please sign this informed consent form.

**(I) Inclusion Criteria**

Subjects can be enrolled in this study only if they meet all the following inclusion criteria:

1.Aged 18-75 years old, regardless of gender;

2.Meet the diagnostic criteria of the International RLS Study Group (for typical RLS) and the expert-confirmed diagnostic criteria for variant RLS;

3.Patients with moderate to severe RLS (IRLS score ≥ 11 points according to the International Restless Legs Syndrome Study Group Severity Rating Scale);

4.Understand and agree to comply with the study protocol, and consent to enrollment and sign the informed consent form.

**(II) Exclusion Criteria**

1.Secondary RLS: such as iron deficiency anemia (serum ferritin < 30 μg/L), renal insufficiency (eGFR < 30ml/min), pregnancy/lactation period, thyroid dysfunction, drug-induced RLS (e.g., antipsychotics, antidepressants that cannot be adjusted);

2.Severe central nervous system diseases (e.g., status epilepticus, severe dementia, stroke within the recent 3 months);

3.Severe cardiovascular diseases (e.g., congestive heart failure, uncontrolled hypertension (systolic blood pressure ≥ 180mmHg or diastolic blood pressure ≥ 110mmHg));

4.Severe hepatic and renal insufficiency (ALT/AST > 3 times the upper limit of normal, eGFR < 30 mL/min/1.73m$^2$ );

5.Active mental illnesses (e.g., schizophrenia, acute episode of bipolar disorder);

6.Drug contraindications: hypersensitivity to Crisugabalin Besilate Capsules or its

excipients;

7.Others: participation in other drug clinical trials within the recent 1 month, inability to cooperate with follow-up (e.g., cognitive impairment, language disorder), history of substance abuse (e.g., alcohol, opioids);

8.Severe cognitive impairment or mental illness that prevents completion of scale assessment;Pregnant or lactating women.

**Research Process**

**Subject Screening and Enrollment Process**

This is a prospective observational cohort study. All enrolled subjects are from the outpatient and inpatient departments of the Department of Neurology in our hospital.

- Screening Site and Source: The study subjects include patients who visit Beijing Friendship Hospital Affiliated to Capital Medical University or participate in research projects related to neurodegenerative diseases.
- Screening Basis: Two neurologists will make clinical diagnosis of RLS and variant RLS according to international guidelines (such as IRLSSG international diagnostic criteria). Pre-enrollment assessment includes preliminary medical history collection, physical and neurological examinations, and strict evaluation in accordance with inclusion and exclusion criteria.

**Information Collection Content and Methods**

The information required for this study includes:

- Demographic information: age, gender, education level, marital status;
- Medical history information: course of main diagnosis, onset time, accompanying symptoms, past medical history, medication history;
- Clinical assessment: International Restless Legs Syndrome Study Group Severity Rating Scale (IRLS), RLS Quality of Life Questionnaire (QoL-RLS);
- Mood, sleep and functional assessment: Hamilton Depression Scale (HAMD); Hamilton Anxiety Scale (HAMA); Activities of Daily Living Scale (ADL); Pittsburgh Sleep Quality Index (PSQI).

**Intervention Measures**

All enrolled patients will be treated with Crisugabalin Besilate Capsules (Manufacturer: [Simeining], Approval Number: [H20240018]), 40mg per dose, twice daily, for oral administration. The treatment cycle is 12 weeks. During the study period, the use of other drugs that may affect the efficacy of this study is prohibited, including neurotransmitter-affecting drugs (antidepressants, antipsychotics, benzodiazepines) and drugs with drug interactions (potent CYP3A4 inhibitors such as ketoconazole, itraconazole, clarithromycin, ritonavir and potent CYP3A4 inducers such as rifampicin, carbamazepine, phenytoin sodium). Continuous oral administration of iron supplements (at a stable dose) is allowed.

**Follow-up**

The severity of patients' symptoms will be assessed before treatment and at Week 2, Week 4, Week 8 and Week 12 of treatment, including the above-mentioned clinical assessment as well as mood, sleep and functional assessment.

3.**How long will this study last?**

Each subject's participation in the study will last for 12 weeks. You may choose to withdraw from the study at any time without any penalty or loss of any benefits you are entitled to. However, if you decide to withdraw from the study midway, we encourage you to discuss with your doctor first. Considering your safety, a relevant examination may be conducted after withdrawal.

**IV. Risks and Benefits**

1.**What are the risks or adverse reactions of participating in this study?**

The possible risks of participating in this study are as follows. You should discuss these risks with your research doctor, or your regular doctor if you wish. During the study, you may experience some, all, or none of these adverse reactions:

**Common Adverse Reactions (Relatively high incidence, tolerable in most patients, and mostly alleviated after drug withdrawal)**

- Nervous system reactions: dizziness, drowsiness and fatigue are relatively common,

which may affect daily activities (such as driving and operating machinery); a few patients may experience inattention, memory impairment, etc., which usually occur at the initial stage of medication and gradually alleviate as the body adapts.

- Digestive system reactions: nausea, dry mouth and constipation are occasionally seen, which generally do not affect continued medication. It is recommended to take the medicine after meals to reduce gastrointestinal discomfort.
- Others: some patients may experience headache and dizziness, mostly mild to moderate, which is related to the slight regulatory effect of the drug on the central nervous system.

**Rare Adverse Reactions (Low incidence, need to be vigilant and inform researchers in a timely manner)**

- Abnormal mental and emotional reactions: a few patients may experience irritability, anxiety, insomnia and other symptoms, especially those with a history of mental illness need to be focused on; in extremely individual cases, depression may occur, which requires immediate drug withdrawal and medical treatment.
- Skin reactions: rash, pruritus and other allergic manifestations are occasionally seen. If skin erythema and swelling or rash spreading occur, please inform the research team in a timely manner for symptomatic treatment.
- Cardiovascular system reactions: palpitations and slight blood pressure fluctuations are rare. Hypertensive patients need to monitor blood pressure regularly during medication.

**Rare but Severe Adverse Reactions (Extremely low incidence, need emergency treatment)**

- Severe central nervous system reactions: in extremely rare cases, confusion and ataxia (unsteady walking, uncoordinated movements) may occur, which requires immediate drug withdrawal and medical treatment.
- Allergic reactions: severe allergic reactions (such as dyspnea, laryngeal edema) are extremely rare, but emergency rescue is required once they occur.

- Withdrawal reactions: although this drug has low addiction potential, sudden withdrawal after long-term medication may cause mild withdrawal symptoms such as insomnia, irritability and muscle soreness. After the end of the study, the doctor will guide the gradual dose reduction to stop the drug to avoid such risks.

**Special Risk Reminder for Off-label Use**

The above adverse reactions are based on the clinical trial data of Crisugabalin Besilate Capsules for its approved indications. The use of this drug in the treatment of RLS (typical and variant types) in this study is an off-label use. There is no sufficient large-sample data to support the occurrence of adverse reactions in RLS patients, and there may be unknown special adverse reactions related to RLS condition. The research team will closely monitor your physical condition throughout the study, and take timely intervention measures once discomfort occurs.

**For Female Subjects**

Pregnancy during participation in the study will pose significant risks to the unborn child, some of which are unpredictable at present. Therefore, this study will not recruit pregnant women as subjects. If you are of childbearing age (including within 1 year after menopause), a pregnancy test (requiring venous blood collection) will be performed on you, and you can only continue to participate in the study if the test result is negative. If you are sexually active, you must agree to take appropriate contraceptive measures during the study and for several months thereafter (please specify the time if possible). If you become pregnant during the study, please immediately inform your research doctor.

2.**What are the benefits of participating in the study?**

If you agree to participate in this study, you may obtain direct medical benefits.

**(1) Symptom Relief and Quality of Life Improvement**

Crisugabalin Besilate Capsules used in this study is a novel highly selective calcium channel modulator, which is expected to effectively alleviate the symptoms related to your RLS (including typical and variant types). These symptoms include crawling sensation, burning sensation, pain and other discomforts in the legs and other affected

parts (such as abdomen, chest, oral cavity, etc.). It can reduce the frequency of symptom attacks in the evening or night, help you improve sleep quality, relieve insomnia, anxiety, depression and other problems caused by the disease, and enhance daily activity ability and overall quality of life. Due to individual differences in drug response, and this study is an exploratory study of off-label use of Crisugabalin Besilate Capsules for RLS and its variant types, there is currently insufficient large-sample clinical data support. Therefore, you may experience the following situations: the discomfort in the legs or other affected parts is not significantly relieved after medication, the frequency of symptom attacks is not reduced, and sleep quality is not improved, that is, you do not obtain direct clinical benefits from the study. If the above situations occur, the research doctor will evaluate your condition within 48 hours. After excluding factors such as medication compliance and insufficient dosage, the treatment plan will be adjusted immediately (such as suspending the trial drug and replacing it with conventional clinical treatment drugs). In addition, 3 months of free follow-up consultation will be provided for you, and assistance will be given to connect with the RLS specialist clinic to ensure that your subsequent treatment is not affected, and your routine medical rights and interests will not be affected due to "no benefit obtained".

**(2) Obtaining Professional Disease Monitoring and Diagnosis and Treatment Guidance**

During the study, you will receive comprehensive and regular professional examinations and follow-up provided by the research team, including symptom assessment and physical examination. Researchers will continuously pay attention to your condition changes and medication reactions, and adjust the intervention plan in a timely manner. This will enable standardized and detailed management of your condition. Especially in the current situation where there is no unified treatment standard for variant RLS, you can obtain personalized diagnosis and treatment suggestions.

**(3) Obtaining Relevant Medical Services Free of Charge**

All study-related medical services such as follow-up visits during the study are free of

charge, which can reduce your medical expenditure burden. In addition, the research team is composed of professional medical staff. If you encounter any health problems during the study, you can obtain professional medical help in a timely manner.

We hope that the information obtained from your participation in this study will benefit patients with the same condition as yours in the future.

**Follow-up Recommendations for Trial Medication**

After the end of the study (12-week treatment period + 3-month follow-up period), the decision on whether to continue using Crisugabalin Besilate Capsules will be made by the research doctor based on the evaluation results of your efficacy and safety, which is divided into 3 specific situations:

1.**Significant efficacy and good safety** (IRLS score decreased by ≥ 50% compared with baseline after the end of treatment period, without the above adverse reactions): continued medication may be considered; the recommended duration of medication is not more than 6 months (there is no long-term medication safety data at present, so the duration needs to be strictly controlled).

2.**Moderate efficacy** (IRLS score decreased by 30%-50% compared with baseline after the end of treatment period): continuous use of the trial drug is not recommended; the research doctor will replace it with the conventional treatment plan recommended by clinical guidelines (such as dopaminergic drugs, other calcium channel modulators) to avoid long-term use of drugs with uncertain efficacy.

3.**No efficacy or poor safety** (IRLS score decreased by < 30% compared with baseline after the end of treatment period, or adverse reactions occur): the trial drug should be discontinued immediately; the research doctor will formulate an alternative treatment plan for you within 24 hours. If physical discomfort is caused by adverse reactions, free follow-up treatment will be provided until the symptoms are relieved.

4.**Precautions for drug withdrawal**: regardless of the situation, the drug should be withdrawn by gradual dose reduction (for those who have taken the drug for < 3 months, reduce to withdrawal within 2 weeks; for those who have taken the drug for ≥ 3 months,

reduce to withdrawal within 4 weeks) to avoid mild discomfort such as insomnia and irritability caused by sudden withdrawal; follow-up visits will be conducted once a week during the dose reduction period to monitor physical reactions.

**V. Will My Information Be Kept Confidential?**

With the understanding and assistance of you and other subjects, the results of this project may be published in medical journals. However, we will keep your research records confidential in accordance with legal requirements. The personal information of study subjects will be strictly confidential. Your personal information will not be disclosed unless required by relevant laws. When necessary, government regulatory authorities, the hospital ethics committee and other relevant researchers can access your data in accordance with regulations.

**VI. Research Costs and Related Compensation**

**1.Costs of Drugs and Related Examinations Used in the Study**

You do not need to pay for questionnaire assessments.

**2.Compensation for Participating in the Study**

There is no compensation involved in participating in this study.

**3.Compensation in Case of Injury**

If you suffer an injury related to this study, you can obtain necessary medical care provided by Beijing Friendship Hospital Affiliated to Capital Medical University. After identification by relevant units in accordance with relevant Chinese laws, compensation/indemnification will be made in accordance with relevant laws and regulations.

**VII. Subject Rights**

Throughout the study, your participation is voluntary. If you decide not to participate in this study, it will not affect other treatments you are entitled to. If you decide to participate, you will be required to sign this written informed consent form. You have the right to withdraw from the trial at any stage without discrimination or unfair treatment, and your corresponding medical treatment and rights will not be affected.

If you experience severe adverse reactions, or your research doctor deems that continuing to participate in the study is not in your best interest, he/she will decide to withdraw you from the study. Without your consent, the sponsor or regulatory authority may terminate the study at any time during the research period. The reasons include complicated other serious diseases and acute exacerbation of the original disease. If this happens, we will notify you in a timely manner, and your research doctor will discuss other options available to you. No new data related to you will be collected in the future. The previously collected research data and the data of those who withdrew due to adverse reactions will be kept confidential.

**IX. Subject Responsibilities**

As a subject, you need to provide true information about your medical history and current physical condition; inform the research doctor of any discomfort found during the study; refrain from taking restricted drugs and foods that the doctor has informed you of; inform the research doctor whether you have recently participated in other studies or are currently participating in other studies.

**X. Who Should I Contact If I Have Questions or Difficulties?**

If you have any questions related to this study, please contact Dr. Wenlu Zhao at 13017688128. If you have any questions related to your rights and interests, or want to report difficulties, dissatisfaction and concerns encountered during the participation in this study, or want to provide opinions and suggestions related to this study, please contact the Bioethics Committee of Beijing Friendship Hospital Affiliated to Capital Medical University at 010-63139006.

**Researcher's Notification Statement**

"I have informed the subject of the research background, purpose, steps, risks and benefits of the study titled *Efficacy and Safety Observation of a Novel Calcium Channel Modulator in the Treatment of Patients with Restless Legs Syndrome and Its Variant Types*, given him/her sufficient time to read the informed consent form, discuss with others, and answered his/her questions about the study; I have informed the subject that

he/she can contact Dr. Wenlu Zhao at any time when encountering problems related to the study, and contact the Bioethics Committee of Beijing Friendship Hospital at any time when encountering problems related to his/her rights and interests, and provided accurate contact information; I have informed the subject that he/she can withdraw from this study; I have informed the subject that he/she will receive a copy of this informed consent form with the signatures of both him/her and me."

Signature of Researcher Who Obtained Informed Consent: _____ Date: _____

**Subject's Informed Consent Statement**

"I have been informed of the background, purpose, steps, risks and benefits of the study titled *Efficacy and Safety Observation of a Novel Calcium Channel Modulator in the Treatment of Patients with Restless Legs Syndrome and Its Variant Types*. I have had sufficient time and opportunity to ask questions, and I am satisfied with the answers. I have also been informed of who to contact when I have questions, want to report difficulties and concerns, provide suggestions for the study, or need further information or want to help with the study. I have read this informed consent form and agree to participate in this study. I know that I can withdraw from this study at any time during the research period without any reason. I have been informed that I will receive a copy of this informed consent form with the signatures of both the researcher and me."

Subject's Signature: _____ Date: _____

Subject's Contact Phone Number: _____

(When the subject has insufficient capacity to give informed consent, add or replace the following:)

Guardian's Signature: _____ Relationship with Subject: _____

Guardian's Contact Phone Number: _____ Date: _____