Clinical Research Protocol

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
Principal Investigator	Houzhen Tuo
Version Number	V3.0
Version Date	2026-01-08

1. Research Background

Restless Legs Syndrome (RLS), also known as Willis-Ekbom disease, is a common neurological sensorimotor disorder in clinical practice. Its typical manifestation is an irresistible urge to move the legs. Symptoms mostly occur in the evening or at night, worsen during rest or inactivity, and can be relieved by movement. RLS seriously affects patients' quality of life, especially leading to insomnia, depression and anxiety[1]. Patients describe various uncomfortable sensations, such as crawling, creeping, burning, distension, pulling, tightness, tearing and even pain[1]. Such discomfort is most prominent in the calves. Current research shows that RLS can involve a wide range of anatomical sites, including the abdomen, bladder, external genitalia, oral/facial region, chest and back. When the discomfort involves body parts other than the lower limbs and meets the diagnostic criteria of the International Restless Legs Syndrome Study Group (IRLSSG)[2], it is referred to as variant RLS[3]. According to the involved sites, variant RLS is classified into subtypes such as restless mouth syndrome[4], restless chest syndrome[5], restless bladder syndrome[6], restless back syndrome[7], restless abdomen syndrome[8], restless arms syndrome[9], and restless genital syndrome[10]. In addition, studies have shown that both the legs and other body parts can be involved simultaneously in RLS patients[11].

At present, drug treatments for typical RLS[12-13] are as follows: dopaminergic drugs are the first-line option for moderate to severe patients, such as non-ergot dopamine receptor agonists including pramipexole and ropinirole. These drugs relieve symptoms by regulating dopamine function in the brain. However, in clinical practice, some patients experience decreased efficacy (commonly observed after 6-12 months of medication), and some patients discontinue treatment due to adverse reactions like nausea and impulse control disorders. Alternative treatments include calcium channel modulators (e.g., gabapentin enacarbil, gabapentin, pregabalin) and opioid drugs, which are applicable for patients intolerant to dopaminergic drugs. Nevertheless, gabapentin has limited effect on improving sleep efficiency and is associated with

common side effects such as dizziness, drowsiness and fatigue. Opioid drugs are only used for refractory cases due to the risk of addiction, with their clinical application subject to strict restrictions. For secondary factors such as iron deficiency, oral iron supplements can alleviate symptoms but are ineffective in non-iron-deficient patients. Due to the lack of unified and standardized diagnostic criteria for variant RLS, its treatment regimens are mostly referenced from those for typical RLS, which have significant limitations: uncertain efficacy and insufficient evidence support. Current treatment studies on variant RLS are mostly case reports or small-sample observations. Clinical treatment often relies on physicians' experience, resulting in poor treatment standardization.

Crisugabalin Besilate Capsules is a novel calcium channel modulator (the third-generation calcium channel modulator). It is a structural derivative of the neurotransmitter γ -aminobutyric acid, featuring an innovative tricyclic cage structure that enhances molecular rigidity. It has high target selectivity and binding affinity for the α 2 δ subunit of voltage-gated calcium channels in the central nervous system. By reducing calcium influx into neurons, it decreases the release of excitatory neurotransmitters such as glutamate and norepinephrine, thereby effectively controlling neuropathic pain. It has shown potential in the treatment of neuropathic pain[14]. As a new-generation highly selective α 2 δ ligand, Crisugabalin Besilate Capsules is expected to become a new option for RLS treatment. At present, data on the efficacy and safety of this drug in the clinical treatment of RLS (especially variant RLS) are limited. Therefore, this study intends to enroll patients with typical RLS and variant RLS, treat them with Crisugabalin Besilate Capsules, and systematically evaluate the efficacy and safety of the drug. This will not only provide a potential treatment option for patients with variant RLS, but also fill the research gap in this field and offer evidence-based basis for the update of clinical diagnosis and treatment guidelines.

[1] Sleep Group of Neurology Physicians Branch of Chinese Medical Doctor Association, Sleep Disorders Group of Neurology Branch of Chinese Medical Association, Sleep Disorders Professional Committee of Chinese Sleep Research

Society. Guidelines for the diagnosis and treatment of restless legs syndrome in China (2021 edition)[J]. Chinese Medical Journal, 2021, 101(13): 908-925.

[2] Allen RP, Picchietti DL, Garcia-Borreguero D, et al. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria--history, rationale, description, and significance. Sleep Med. 2014;15(8):860-873.

[3] Turrini A, Raggi A, Calandra-Buonaura G, Martinelli P, Ferri R, Provini F. Not only limbs in atypical restless legs syndrome. Sleep Med Rev. 2018;38:50-55.

[4] Jung Y, Hassan A, St Louis EK, Robertson CE. Restless mouth syndrome. Neurol Clin Pract. 2017;7(3):e29-e30.

[5] Ishizuka K, Ohira Y. Restless Chest Syndrome: A Rare Variant of Restless Legs Syndrome. Eur J Case Rep Intern Med. 2022;9(7):003398.

[6] Antelmi E, Coccagna G, Ferini-Strambi L, Marelli S, Provini F. 'Restless bladder' and the boundaries of the restless legs syndrome. Eur J Neurol. 2013;20(11):e128.

[7] Sun F, Tao H, Jin W. Restless Back Syndrome: A Case Report and Literature Review. Psychiatry Clin Psychopharmacol. 2022;32(4):351-354. Published 2022 Dec 1.

[8] Pérez-Díaz H, Iranzo A, Rye DB, Santamaría J. Restless abdomen: a phenotypic variant of restless legs syndrome. Neurology. 2011;77(13):1283-1286.

[9] Webb AT. Letter: Restless arms syndrome. JAMA. 1976;236(7):822.

[10] Waldinger MD, Schweitzer DH. Persistent genital arousal disorder in 18 Dutch women: Part II. A syndrome clustered with restless legs and overactive bladder[J]. J Psychosom Obstet Gynaecol, 2003,24(4):221-229.

[11] Suzuki K, Suzuki S, Miyamoto M, et al. Involvement of legs and other body parts in patients with restless legs syndrome and its variants. J Neurol Sci.

[12] Trenkwalder C, Allen R, Högl B, et al. Comorbidities, treatment, and pathophysiology in restless legs syndrome. Lancet Neurol. 2018;17(11):994-1005.

[13] Sleep Group of Neurology Physicians Branch of Chinese Medical Doctor Association, Sleep Disorders Group of Neurology Branch of Chinese Medical Association, Sleep Disorders Professional Committee of Chinese Sleep Research

Society. Guidelines for the diagnosis and treatment of restless legs syndrome in China (2021 edition)[J]. Chinese Medical Journal, 2021, 101(13): 908-925.

[14] Expert Group of Guidelines for the Treatment of Diabetic Peripheral Neuropathic Pain with Crisugabalin. Guidelines for the Treatment of Diabetic Peripheral Neuropathic Pain with Crisugabalin[J]. International Journal of Endocrinology and Metabolism, 2024, 44(06): 446-449.

2. Research Objectives

The main objective 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, 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.

3. Research Content

This study plans to adopt a prospective observational cohort study design and enroll outpatients diagnosed with RLS and its variant types in the Department of Neurology. All patients will be treated with Crisugabalin Besilate Capsules. Through baseline visit and follow-up visits at Week 2, Week 4, Week 8 and Week 12 after treatment, the study will systematically collect patients' scores of the International Restless Legs Syndrome Rating Scale (IRLS), sleep quality and quality of life, and closely monitor drug-related adverse events. The study aims to objectively evaluate the efficacy and safety of the 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.

4. Research Protocol

4.1 Study Design Type

Experimental prospective single-arm study

4.2 Study Subjects

4.2.1 Study Population

Subjects admitted to the outpatient department or inpatient ward of the Department of Neurology, Beijing Friendship Hospital Affiliated to Capital Medical University.

4.2.2 Study Center

Beijing Friendship Hospital Affiliated to Capital Medical University

4.2.3 Planned Enrollment

A total of 20 subjects are planned to be enrolled in the study, including patients with RLS and variant RLS.

4.2.4 Inclusion and Exclusion Criteria

(1) 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 Rating Scale);

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

(2) 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.

4.3 Research Process

4.3.1 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.

4.3.2 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).

4.3.3 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.

4.3.4 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.

4.4 Observation Indicators

This study adopts a prospective observational cohort study design, enrolls patients with RLS and variant RLS, treats them with Crisugabalin Besilate Capsules, and objectively evaluates the efficacy and safety of this novel calcium channel modulator.

(1) Primary Outcome Measures (Tier 1 Indicators)

Evaluate the change in IRLS score of patients with RLS after 12 weeks of treatment with Crisugabalin Besilate Capsules compared with the baseline. Calculate the change value and response rate of IRLS score before and after treatment (response rate = (score before treatment - score after treatment)/score before treatment × 100%). A response rate ≥ 50% is defined as treatment effective.

(2) Secondary Outcome Measures (Tier 2 Indicators)

1.Evaluate the improvement effect of Crisugabalin Besilate Capsules on patients' sleep quality (using the Pittsburgh Sleep Quality Index (PSQI) or relevant scales).

2.Evaluate the improvement effect of Crisugabalin Besilate Capsules on patients' quality of life (using general scales such as the RLS Quality of Life Questionnaire (RLS-QoL)).

3.Evaluate the improvement effect of Crisugabalin Besilate Capsules on patients' mood (using general scales such as HAMA and HAMD).

4.Evaluate the incidence, severity and outcome of drug-related adverse events during

treatment.

4.5 Sample Size Determination

This study is a prospective single-arm observational cohort, with the primary endpoint set as "the change value of total IRLS score at Week 12 of treatment compared with baseline (continuous variable)". Referring to a published double-blind, crossover controlled study on gabapentin (also a calcium channel modulator) for the treatment of RLS (doi: 10.1212/WNL.59.10.1573), after 6 weeks of active treatment in 24 RLS patients in that study, the mean IRLS score decreased by 8.4 points (SD ≈ 6.1 points). Assuming that Crisugabalin Besilate Capsules has equivalent efficacy at the conventional dose, the parameters of this study are set as follows: expected decrease value δ = 8.4 points, standard deviation of paired differences σ = 6.1 points, two-sided α = 0.05, power 1-β = 90%. Using the sample size formula for paired t-test:

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 \cdot \sigma^2}{\delta^2}$$

The basic sample size n = 17 cases is obtained. Considering that the dropout rate of observational design is higher than that of RCT (estimated 15%) and the data quality disqualification rate is 5%, it is expected to complete 20 cases, which can meet the statistical robustness when the overall primary endpoint power is ≥ 90% and the dropout rate is < 20%.

4.6 Informed Consent

Informed consent form must be signed.

4.7 Risk Control and Management Measures

1.Risk of drug-related adverse events: Based on existing data, the study drug Crisugabalin Besilate Capsules may cause common adverse reactions such as dizziness, drowsiness and fatigue. Control measures: Clearly inform all potential common adverse reactions in the Informed Consent Form. Actively inquire about and record all adverse events using non-leading questions during each follow-up visit, and document in detail the occurrence time, severity, frequency, measures taken and outcome of each adverse event. In case of serious adverse events, researchers will

immediately conduct medical treatment and report to the Institutional Ethics Committee within 24 hours. Meanwhile, assist subjects in obtaining corresponding medical compensation.

2.Risk of privacy leakage: The medical information and scale data collected during the study involve personal privacy. Control measures: Assign a unique identification code to each subject, and mark all study data with codes. Electronic data are stored in encrypted form, and paper documents are kept under lock and key. Access rights are strictly restricted to authorized researchers. When publishing research results in the future, ensure that no personally identifiable information is included.

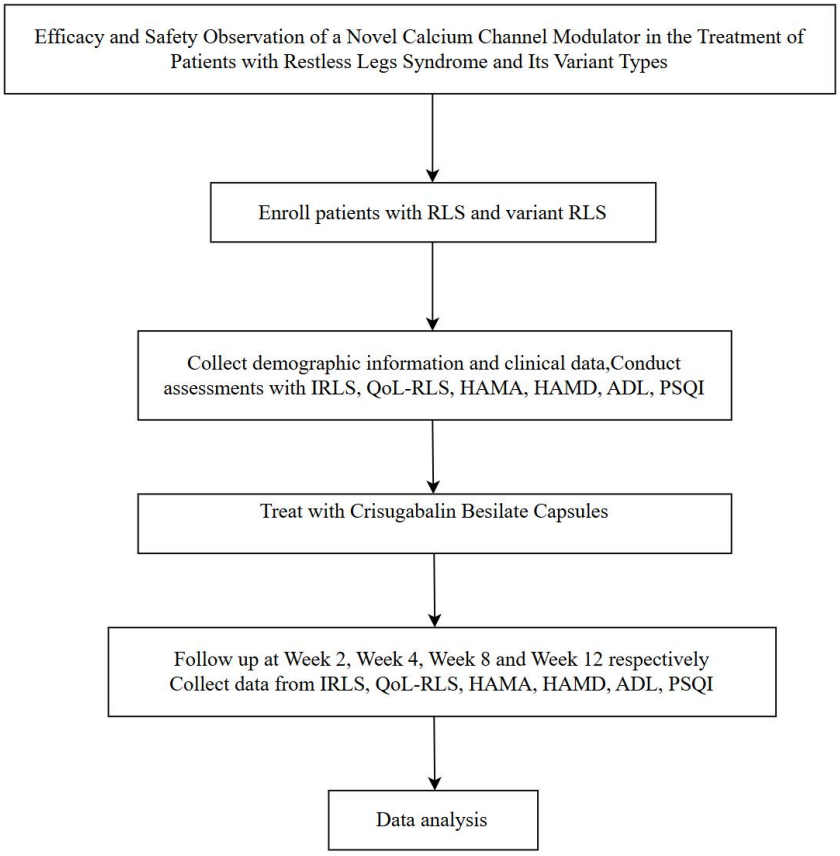
3.Study-related discomfort and burden: Multiple follow-up visits and scale filling may bring time burden and mild discomfort to subjects. Control measures: Clearly explain the study process and required time to subjects before the start of the study. Arrange follow-up visit time as far as possible according to the convenience of subjects. Clearly inform subjects that they have the right to withdraw from the study unconditionally at any time, and their medical rights and interests will not be affected.

4.Risk of protocol deviation and dropout: Subjects may fail to follow up as planned or withdraw from the study, resulting in data loss. Control measures: Establish a good relationship: maintain good communication with subjects and remind them of follow-up dates. Record in detail the reasons for all dropped cases, and adopt appropriate methods to handle missing data in the final statistical analysis and evaluate its impact on the results.

4.8 Confidentiality of Research Information

The personal information of all enrolled subjects will be processed, stored and used in a de-identified manner. All clinical data will be reviewed and preserved by the study sponsor. Only the research team members designated by the study sponsor can access the personal information and clinical data related to the subjects. The information and data generated during the study will be properly kept in accordance with regulations. The publication of research results after the completion of the study will not disclose the personal information of the subjects.

5. Technical Route



6. Statistical Methods

Data analysis in this study will be performed using SPSS and Graphpad Prism software. For measurement data, if they conform to normal distribution, they will be described by mean±standard deviation; if they do not conform to normal distribution, they will be described by median (interquartile range). For count data, they will be described by case number (percentage). For before-and-after comparison of a single group, measurement data will first undergo normality test (Shapiro-Wilk method). If the data conform to normal distribution, paired t-test will be used for data analysis; if not, non-parametric Wilcoxon signed-rank test will be adopted. McNemar test will be used for count data. A P value < 0.05 will be considered statistically significant for all statistical difference analyses.

7. Quality Control

1.Subject screening and enrollment: This study is carried out relying on the Department of Neurology of our hospital, which has well-equipped scientific research and clinical platforms. The Department of Neurology has a high-level diagnosis and

treatment team for sleep disorders and movement disorders, with experience in participating in many large-scale domestic and foreign clinical studies. The outpatient clinic for sleep disorders and movement disorders receives more than 300 patients including those with RLS every month, among which 10-15 are new patients, ensuring the enrollment of a sufficient number of eligible clinical subjects and healthy controls for the study. All researchers in this study have received GCP training and obtained certificates, and have passed consistency training on scales such as IRLS, PSQI and CGI-I to ensure assessment quality.

2.Quality control measures during the study: Establish a clear subject screening path to ensure that each enrolled patient strictly meets the inclusion and exclusion criteria, and retain the original signed Informed Consent Form. All scale assessments and fillings must be completed on-site during the visit to avoid recall bias. Follow-up management: Set up a special follow-up reminder system (such as telephone and short message appointment) to minimize the loss of follow-up. For any dropped subject, the reason must be recorded and every effort should be made to find out the cause of dropout.

3.Ethical and compliance supervision: The entire research process is subject to the supervision and review of the Institutional Ethics Committee. Any modification to the study protocol must be reported to the Ethics Committee for approval before implementation.

8. Qualifications and Division of Labor of Team Members

Name	Qualification	Department	Division of Labor
Houzhen Tuo	Chief Physician	Department of Neurology	Overall coordination, protocol formulation, etc.
Xinran Xu	Resident Physician	Department of Neurology	Subject screening and enrollment review, handling of emergencies
Wenlu Zhao	PhD Candidate	Department of Neurology	Signing of informed consent form, data collection and analysis
Shiya Wang	PhD Candidate	Department of Neurology	Signing of informed consent form, data collection
Ying Cui	PhD Candidate	Department of Neurology	Signing of informed consent form, data collection
Bingyu Han	PhD Candidate	Department of	Signing of informed consent form, data

		Neurology	collection
Xiaolong Ma	Master Candidate	Department of Neurology	Signing of informed consent form, data collection
Sichen Wang	Master Candidate	Department of Neurology	Signing of informed consent form, data collection
Hao Zheng	Master Candidate	Department of Neurology	Signing of informed consent form, data collection