Journal of Pain Research

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STUDY PROTOCOL

# The Efficacy and Safety of Crisugabalin (HSK16149) in Fibromyalgia Patients: Protocol for a Prospective Randomized Open Blinded-Endpoint (PROBE) Study

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**Background:** Fibromyalgia (FM) is a chronic condition, imposing a substantial burden on patients. Pregabalin, a first-line treatment, offers incomplete efficacy for many and is associated with dose-limiting central nervous system adverse effects. Crisugabalin is a novel α2δ ligand with 23-fold higher binding affinity than pregabalin and has shown potentially fewer central nervous system adverse effects in animal models. While crisugabalin has shown efficacy in other neuropathic pain conditions, its efficacy in FM, particularly in a direct comparison with pregabalin, remains unclear.

**Methods and Analysis:** This multicenter, prospective, randomized, pregabalin-controlled, open-label, blinded-endpoint study will be conducted at 10 hospitals in China. A total of 1116 adult patients with FM and a baseline average daily pain intensity of ≥4 on an 11-point numerical rating scale will be enrolled. Participants will be randomly assigned (1:1) to receive either crisugabalin or pregabalin for 12 weeks using a standardized, flexible-titration protocol. While participants and treating physicians will be aware of the treatment allocation, outcome assessors and data analysts will remain blinded. The primary outcome is the proportion of patients achieving at least a 50% reduction in average pain intensity from baseline at week 12. Secondary outcomes include pain intensity measures, study drug dosing and rescue analgesic utilization, Revised FM Impact Questionnaire, Brief Pain Inventory severity and interfere subscales, short-form 36 Health Survey, Patient Global Impression of Change Scale, Medical Outcomes Study Sleep Scale, Beck Depression Inventory-II, and incidence of adverse events. Analyses will be performed on the modified intention-to-treat and per-protocol populations.

**Ethics and Dissemination:** This study, approved by the Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University (KY2025-217-03), will be conducted in accordance with the Declaration of Helsinki. Written informed consent will be obtained from all participants, and findings will be disseminated through peer-reviewed publications and scientific conferences.

**Trial Registration:** Clinical Trials.gov identifier: NCT07196657. Registered on September 29, 2025 (https://www.clinicaltrials.gov/search?term=NCT07196657).

**Keywords:** fibromyalgia, crisugabalin, pregabalin, blinded-endpoint, randomized controlled trial

https://doi.org/10.2147/JPR.S580694
Received: 2 December 2025
Accepted: 19 February 2026
Published: 3 March 2026

## Introduction

Fibromyalgia (FM) is a chronic and multifaceted condition characterized by widespread pain lasting at least three months, along with a series of debilitating symptoms such as fatigue, sleep disturbances, cognitive impairment, anxiety, depression, and muscle stiffness.[1] FM is one of the most common causes of chronic widespread pain, affecting approximately 1.2% to 5.4% of the general population, with a striking female-to-male ratio of about 3:1.[2] Prevalence increases with age, peaking between 50 and 60 years, and it ranks as the third most common musculoskeletal condition globally, following lumbar pain and osteoarthritis.[3] This disorder places a substantial burden on individuals and society, leading to elevated healthcare costs, reduced productivity, and significant disability.[4]

Management of FM necessitates a multimodal approach that integrates non-pharmacological and pharmacological strategies, as recommended by guidelines such as those from the European League Against Rheumatism.[5,6] Non-pharmacological strategies include patient education, physical fitness, and psychotherapy.[6] While these therapies are often effective for patients with mild symptoms, a substantial proportion of patients require additional pharmacological treatments to achieve adequate symptom relief.[7] Medications commonly used include anticonvulsants,[8,9] antidepressants,[10,11] muscle relaxants,[12] and others.

Pregabalin, a γ-aminobutyric acid analog, binds to α2δ subunits of voltage-dependent calcium channels in the central nervous system, reducing calcium ion influx and subsequently inhibiting the release of excitatory neurotransmitters such as glutamate, norepinephrine, and substance P.[13] Pregabalin is the only anticonvulsant approved by the United States Food and Drug Administration and is one of the first-line drugs for the treatment of FM.[14] Clinical trials have demonstrated that pregabalin significantly reduces both pain and sleep disturbance in patients with FM.[15–17] A Cochrane review reported that 39% to 43% of participants achieved at least a 30% reduction in pain intensity after 12 or 13 weeks of stable treatment with pregabalin at dose of 300 to 600 mg per day.[15] While this suggests that pregabalin provides effective pain relief for some patients, it does not benefit all patients equally. Additionally, pregabalin is associated with systemic and notable central nervous system adverse effects, including somnolence, dizziness, and dry mouth.[18] At the dose of 600 mg per day, approximately 20% of patients discontinued treatment due to adverse effects.[15] These limitations underscore the unmet need for novel calcium channel blockers with enhanced efficacy and less neurotoxic effects for the treatment of FM.

Crisugabalin (HSK16149), similar to pregabalin, is an oral γ-aminobutyric acid analog that binds to the calcium channel α2δ subunits, reducing the calcium influx of voltage-dependent calcium channels in the central nervous system and consequently decreasing the release of excitatory neurotransmitters.[19] Compared to pregabalin, crisugabalin demonstrates a 23-fold higher affinity for the α2δ subunit in vitro binding studies, along with a higher or equivalent therapeutic index and fewer central nervous system adverse effects in animal models.[19] These properties suggest that crisugabalin could be a promising drug alternative to pregabalin. In a randomized clinical trial, crisugabalin significantly reduced the average daily pain score at week 13 compared with placebo in Chinese patients with diabetic peripheral neuropathic pain, with most treatment-emergent adverse events being mild to moderate.[20] Similarly, a Phase 3 randomized clinical trial suggested that crisugabalin significantly improved pain scores and was well tolerated over placebo in adults with postherapetic neuralgia.[21] Additionally, a study evaluating the safety, tolerability, and pharmacokinetics of crisugabalin in healthy Chinese subjects revealed that it was safe and generally well tolerated after single or multiple administration.[22] However, to date, no studies have investigated the efficacy of crisugabalin in patients with FM, nor have there been any direct comparisons of the efficacy and safety of crisugabalin and pregabalin for the treatment of chronic pain.

Therefore, we hypothesize that crisugabalin may offer a therapeutic efficacy comparable to pregabalin, potentially with a more favorable adverse effect profile. To test this hypothesis, we will conduct a multicenter, prospective, randomized, open-label blinded-endpoint (PROBE) study. To our knowledge, this study represents the first direct head-to-head randomized trial comparing crisugabalin with pregabalin in patients with FM.

## Materials and Methods

### Study Design

A multicenter, prospective, randomized, pregabalin-controlled, open-label, blinded-endpoint study will be conducted in the 10 different hospitals to compare the efficacy and safety of crisugabalin with pregabalin for the treatment of FM. The

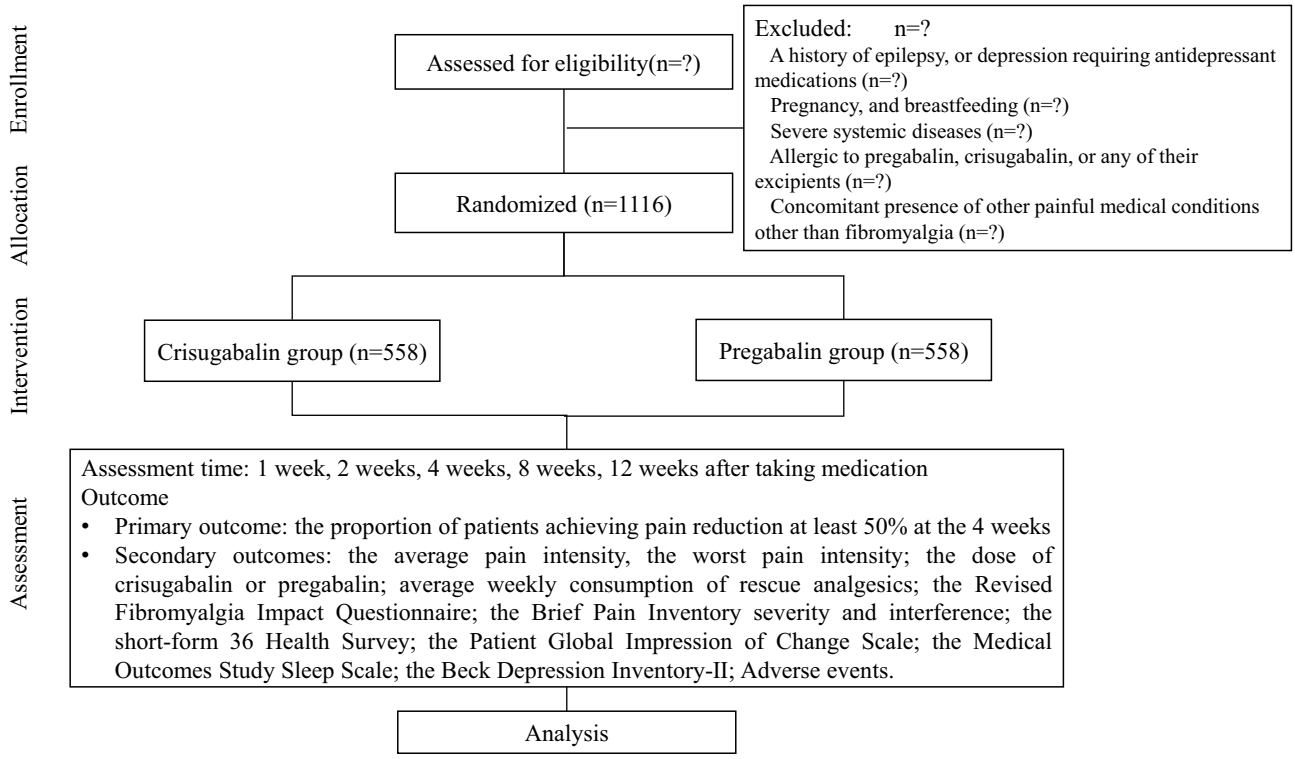


**Figure 1** Flowchart of enrollment, allocation, intervention, and assessment.

study will be conducted at Department of Pain Management, Beijing Tiantan hospital, Yanbian University Hospital, Fourth Affiliated Hospital of Harbin Medical University, First Hospital of Lanzhou University, Second Hospital Affiliated to University of South China, Xiangya Hospital of Central South University, Zhongnan Hospital of Wuhan University, China–Japan Friendship Hospital, Peking University Third Hospital, First Affiliated Hospital of Nanchang University. This study will be conducted in accordance with the principles of the Declaration of Helsinki. Ethics approval for the trial was obtained from the Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University (reference number: KY2025-217-03). This trial was registered at ClinicalTrials.gov (NCT07196657) before patient enrollment. All methods and results will be reported according to Consolidated Standards of Reporting Trials guidelines. The flowchart is briefly illustrated in Figure 1. And all trial procedures are summarized in Table 1.

**Table 1** The Schedule of Enrollment, Interventions, and Assessments

| | −1 Day | 0 Day | Week 1 | Week 2 | Week 4 | Week 8 | Week 12 |
|---|---|---|---|---|---|---|---|
| **Enrollment** | | | | | | | |
| Eligibility screening | ✓ | | | | | | |
| Informed consent | ✓ | | | | | | |
| Allocation | | ✓ | | | | | |
| **Intervention** | | | | | | | |
| Crisugabalin group | | ✓ | | | | | |
| Pregabalin group | | ✓ | | | | | |

(*Continued*)


https://doi.org/10.2147/JPR.S580694

**Table 1** (Continued).

| | −1 Day | 0 Day | Week 1 | Week 2 | Week 4 | Week 8 | Week 12 |
|---|---|---|---|---|---|---|---|
| **Assessment** | | | | | | | |
| Baseline data | ✓ | | | | | | |
| Proportion of responders achieving ≥ 50% reduction from baseline in average pain intensity* | | | | | | | ✓ |
| Average pain intensity | | | ✓ | ✓ | ✓ | ✓ | ✓ |
| Worst pain intensity | | | ✓ | ✓ | ✓ | ✓ | ✓ |
| Dose of crisugabalin or pregabalin | | | ✓ | ✓ | ✓ | ✓ | ✓ |
| Average weekly consumption of rescue analgesics | | | | | ✓ | ✓ | ✓ |
| Revised FM Impact Questionnaire | | | | | ✓ | ✓ | ✓ |
| Brief Pain Inventory severity subscale | | | | | ✓ | ✓ | ✓ |
| Brief Pain Inventory interfere subscale | | | | | ✓ | ✓ | ✓ |
| Short-form 36 Health Survey | | | | | ✓ | ✓ | ✓ |
| Patient Global Impression of Change Scale | | | | | | | ✓ |
| Medical Outcomes Study Sleep Scale | | | | | ✓ | ✓ | ✓ |
| Beck Depression Inventory-II | | | | | ✓ | ✓ | ✓ |
| Adverse events | | | ✓ | ✓ | ✓ | ✓ | ✓ |

**Notes**: ✓ indicates the scheduled performance of the procedure or assessment at the corresponding visit; blank cells indicate that the procedure or assessment is not scheduled. *Primary outcome.
**Abbreviation**: FM, Fibromyalgia.

## Recruitment and Informed Consent

Experienced attending doctors will enroll patients with FM at the Department of Pain Management. All the candidates will be informed in detail of the following information: the purpose of the study, interventions, benefits, possible risks, and corresponding responses. Candidates will be given at least 1 hour to consider whether or not to participate in the study. Written informed consent will be obtained from all patients. Participants will be able to withdraw from the study at any time, and they will be clearly informed that their relationship with the healthcare provider would not be affected.

## Participants

### Inclusion Criteria

1. Diagnosed with FM, based on the 2016 Revisions to the 2010/2011 FM diagnostic criteria;
2. Aged over 18 years old;
3. Suffering from moderate to severe FM, refractory to non-pharmacological interventions and without prior exposure to recommend pharmacological treatments for FM;
4. Average daily pain intensity of at least 4 over 7 days on the numerical rating scale (NRS) at baseline;
5. Aspartate aminotransferase and alanine aminotransferase concentrations lower than twice the upper limit of normal;
6. Estimated glomerular filtration rate of 30 mL/min per 1·73 $m^2$ or higher;
7. Has sufficient cognitive and language skills to be able to comply with all the study requirements.

### Exclusion Criteria

1. A history of epilepsy, or depression requiring antidepressant medications;

2. Pregnancy, and breastfeeding;
3. Severe systemic disease, such as poorly controlled hypertension, poorly controlled diabetes mellitus, or cardiac arrhythmias and conduction abnormalities on 12-lead electrocardiogram at baseline;
4. Allergic to pregabalin, crisugabalin, or any of their excipients;
5. Concomitant presence of other painful medical conditions other than FM.

### Withdrawal Criteria

1. Experiences severe adverse events (AEs) during the treatment phase.

## Randomization and Masking

Allocation concealment will be achieved with site staff using an online platform (https://www.sealedenvelope.com). The trial statistician will create predetermined randomization schedule stratified by site using permuted blocks size of four. Participants with FM will be randomly assigned with crisugabalin group or pregabalin group at 1:1 ratio.

This will be an open-label trial, so the participants and treating physician will be aware of the treatment arms and the dose level. Those assessing outcomes and analyzing data will be masked to the treatment group.

## Procedures

To minimize confounding effects and ensure that observed therapeutic changes are attributable to the study medication, the use of concomitant analgesic therapies will be restricted throughout the 12-week trial period. This includes procedural interventions (eg, nerve blocks, acupuncture), and any newly initiated programs like cognitive-behavioral therapy or structured exercise regimens. Only stable, pre-existing nonpharmacological treatments if initiated at least four weeks prior to screening will be permitted. Acetaminophen will be permitted as rescue medication for FM-related pain, at doses up to 1000 mg per administration and not exceeding 3000 mg per day.[23] All rescue medication use, including dose and frequency, will be recorded prospectively.

All participating hospitals will adhere to the identical standardized dosage protocol for the prescription of crisugabalin or pregabalin, aiming for an optimal balance of efficacy and tolerability. In the absence of FM-specific dose-ranging studies for crisugabalin, the selected dosing regimen was informed by the approved prescribing information and prior phase 3 clinical trials in neuropathic pain conditions, including diabetic peripheral neuropathic pain and postherpetic neuralgia,[20,21] in which this dose range demonstrated favorable efficacy and tolerability. For the crisugabalin group (Crisugabalin Besilate Capsules, Haisike Pharmaceutical Co. LTD, Sichuan, China), treatment will be initiated at a dose of 20 mg twice daily. If pain remains inadequately controlled after 1 to 2 weeks and the patient exhibits good tolerance to the medication, the dosage may be cautiously escalated to 40 mg twice daily. For the pregabalin group (Pregabalin Capsules, Pfizer Pharmaceutical Co. LTD, New York, U.S.), treatment will begin at 150 mg per day taken in two or three divided doses, titrating to 300 mg per day after 3 to 7 days. Based on response and tolerability, the dose may be further increased in 150 mg per day increments at 3- to 7-day intervals, up to a maximum of 450 mg per day.[24]

AEs and symptoms will be closely monitored at each study contact. Participants whose pain remains inadequately controlled without significant AEs will be escalated according to their assigned schedule, while those achieving satisfactory pain relief will maintain their current effective dose. If a participant experiences intolerable AEs during dose escalation, the dosage will be reduced to the highest previously tolerated level, which will be defined as their maximum tolerated dose. If AEs are intolerable even at the initial dose, the study medication will be discontinued, and the participant will be withdrawn from the trial.

## Follow-Up

The total study duration for each participant will be 12 weeks, commencing after a screening visit. Four follow-up contacts are scheduled at week 1, week 2, week 4, week 8, and week 12. To enhance participant convenience and closely monitor initial response, the week 1 and week 2 visits will be conducted via telephone. These calls will focus on monitoring AEs, assessing initial efficacy, and guiding any necessary dose titration. The week 4, week 8, and week 12 visits will be conducted as in-person evaluations at the outpatient clinic. During these visits,

participants will undergo a comprehensive clinical assessment, a full reassessment of efficacy and safety, pill counts to confirm adherence, and the completion of all study questionnaires and assessment scales.

## Data Management and Quality Assurance

Trained study investigators at each site will collect all participant data using standardized case report forms developed specifically for this protocol. To ensure data accuracy and integrity, all information will be entered into a centralized electronic database (EpiData Manager, Version 4.6.0.6; EpiData Association, Denmark) via an independent double-data entry procedure. Any discrepancies identified during this validation process will be resolved by cross-referencing the original source documents.

An independent Data and Safety Monitoring Committee will be established to provide oversight for the trial. The committee will convene every six months to review cumulative safety and data validity, evaluate the overall conduct of the study, and provide formal recommendations to the steering committee regarding the continuation, modification, or potential termination of the trial.

## Patient and Public Involvement

Patients and the public were not involved in the development of the research question, the study design, or the selection of outcome measures for this protocol. Participants will be recruited from the participating clinical sites via physician referral.

Study findings will be disseminated to the scientific community through presentations at relevant academic conferences and publication in peer-reviewed journals. Participants may request a lay summary of the study results after trial completion.

## Study Outcomes

Participants will record daily pain in paper diaries for the duration of the trial. The primary and secondary endpoints align with the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations for core outcome domains in chronic pain trials.[25]

## Primary Outcome

The primary outcome is the proportion of patients achieving pain relief at the week 12, that is, the proportion of patients whose baseline average pain intensity is reduced by at least 50%. The pain intensity will be measured based on NRS, where 0 represents no pain and 10 represents worst pain imaginable.

## Secondary Outcomes

1. The average pain intensity at week 1, 2, 4, 8, 12.
2. The worst pain intensity at week 1, 2, 4, 8, 12.
3. The dose of crisugabalin or pregabalin at week 1, 2, 4, 8, 12.
4. The average weekly consumption of rescue analgesics at week 4, 8, 12.
5. The Revised FM Impact Questionnaire[26] of week 4, 8, 12.
6. The Brief Pain Inventory severity and interfere subscales[27] at week 4, 8, 12.
7. The short-form 36 Health Survey[28] at week 4, 8, 12.
8. The Patient Global Impression of Change Scale[29] at week 12.
9. The Medical Outcomes Study Sleep Scale[30] at week 4, 8, 12.
10. The Beck Depression Inventory-II[31] at week 4, 8, 12.
11. AEs throughout the study.

## Statistical Analysis

Sample size calculation was performed using the PASS software (V 15.0; NCSS, LLC, USA). The primary efficacy outcome for this study is the proportion of participants achieving at least 50% reduction in average pain from baseline,

measured at week 12. Based on a previous study, the response rate in the pregabalin group was estimated to be approximately 35%.[32] We conservatively assumed a response rate of 45% for the crisugabalin group, corresponding to a clinically meaningful difference of 10% between the two groups. A total sample size of 1116 patients (558 per group) is calculated to provide 90% power to detect this difference. This calculation was based on a two-sided chi-square test with an overall type I error rate of 0.05. This final number accounts for a potential dropout rate of 10%.

Statistical analysis will be performed using SPSS software (V 27.0; IBM Corporation; Armonk, NY, USA). All final conclusions will be determined in line with the intention-to-treat (ITT) principle, adhering to the CONSORT guideline. Efficacy analyses will be performed using both the modified intention-to-treat (mITT) and the per-protocol populations. The mITT population will include all randomized patients who receive at least one dose of crisugabalin or pregabalin and provide at least one assessment of any efficacy parameter after taking the medication. The safety population, which includes all randomized patients who receive at least one dose of the study medication, will be used for all safety analyses.

The primary outcome for this study is the proportion of patients achieving at least 50% pain relief at week 12, calculated from baseline average pain intensity. This primary outcome, along with other categorical variables, will be presented as counts (percentages). Comparisons between the treatment groups for categorical data will be performed using the Chi-square test or Fisher's exact test, as appropriate. In addition, changes in continuous pain intensity over time will be analyzed as supportive analyses using linear mixed-effects models, with treatment group specified as a fixed effect and study center included as a random effect to account for repeated measurements and potential inter-center variability.

Secondary continuous outcomes and other quantitative variables will be summarized using mean ± standard deviation for normally distributed data or median (interquartile range) for skewed distributions. Data normality will be evaluated with the Shapiro–Wilk test. Between-group comparisons will be performed using Student's *t*-test for normally distributed variables or the Mann–Whitney *U*-test for skewed data.

For all analyses, a two-sided P-value $< 0.05$ will be considered statistically significant.

The primary outcome at week 12 will be calculated from daily pain diaries. If a participant has more than 50% of the daily NRS scores missing during week 12, their primary outcome for that participant will be treated as missing. Missing data for the primary outcome will be handled using multiple imputation based on the Markov Chain Monte Carlo method. To assess the robustness of the primary outcome to assumptions about missing data, several sensitivity analyses will be performed. In a "worst-case" scenario, participants in the crisugabalin arm who discontinue the study will be assumed to have no pain relief, while those in the comparator arm who discontinue will be assumed to have favorable outcomes. The inverse will be applied in the "best-case" scenario. Additional pattern-mixture and tipping-point analyses will also be conducted to further evaluate robustness.

Furthermore, pre-specified subgroup analyses will be performed for the primary outcome based on baseline characteristics such as age, gender, course of FM, baseline pain intensity, and baseline Beck Depression Inventory-II score. In addition, selected baseline variables will be explored as potential predictors of treatment response in exploratory analyses. All subgroup and predictor analyses will be considered exploratory and hypothesis-generating, and the study is not powered to detect definitive effects within subgroups. A P-value $< 0.05$ for the interaction term (treatment group × subgroup variable) will be considered statistically significant, suggesting a subgroup effect.

## Discussion

This multicenter, prospective, randomized, controlled trial is designed to compare the efficacy and safety of crisugabalin and pregabalin for patients with FM, using a rigorous design with a relatively large sample size. Given the significant limitations of current non-pharmacological therapies for many FM patients, this study seeks to identify a treatment option with potentially enhanced efficacy and improved tolerability. This research aims to provide new guidance for FM management and potentially expand the therapeutic options for this challenging condition by evaluating the novel compound crisugabalin.

To reconcile methodological rigor with practical feasibility, this trial adopts a PROBE design. A double-blind, double-dummy design is deemed unfeasible primarily due to the asymmetrical titration protocols of the two study

drugs. Crisugabalin requires a simplified titration (20 mg to 40 mg twice daily), whereas pregabalin necessitates multiple adjustments up to 450 mg per day. Implementing a double-dummy setup would have resulted in an excessive pill burden, potentially compromising treatment adherence and increasing the complexity of drug management across multiple clinical sites. To mitigate the expectancy and reporting bias associated with open-label treatment, we employed blinded outcome assessors and standardized daily pain diaries to preserve the scientific integrity of the results.

Furthermore, to prevent selection bias and ensure that confounding factors are distributed evenly between groups, eligible individuals will be randomized 1:1 to either the crisugabalin group or the pregabalin group. This will be managed through a centrally managed, site-stratified scheme. Allocation will be concealed, generated by an independent research assistant not involved in the baseline assessment or follow-up procedures, ensuring impartiality. By combining an open-label design with blinded endpoint assessment, this study design maintains both feasibility and the integrity of its results.

Our endpoint framework aligns with IMMPACT recommendations that chronic pain trials evaluate outcomes across six core domains, including pain, physical functioning, emotional functioning, participant ratings of global improvement and satisfaction, symptoms and adverse events, and participant disposition (eg, adherence and reasons for withdrawal). In this protocol, pain intensity is captured using a NRS recorded in daily diaries, and substantial pain improvement is evaluated using a $\geq$ 50% responder definition, which is widely accepted as representing a clinically meaningful benefit in FM and other chronic pain conditions.[24,33]

The primary outcome, the proportion of patients whose baseline average pain intensity is reduced by at least 50% at 12 weeks, widely accepted as representing a clinically meaningful improvement for patients. The 12-week time point was selected to capture a balance between the rapid onset of action expected from α2δ ligands and the time needed for dose stabilization. Physical functioning is assessed using the Brief Pain Inventory scale, health-related quality of life using the short-form 36 Health Survey, participant ratings of global improvement and satisfaction using the Patient Global Impression of Change Scale, and emotional functioning using the Beck Depression Inventory-II. Symptoms and adverse events are systematically collected throughout follow-up. Participant disposition, including screening, enrollment, adherence, and withdrawals, will be documented and reported in accordance with CONSORT principles. Together, this multidimensional outcome framework is intended to provide a comprehensive and clinically meaningful evaluation of both the efficacy and safety of crisugabalin compared with pregabalin in patients with FM.

Despite its prospective and rigorous design, this study protocol has several constraints. First, the open-label protocol inherently risks introducing performance or ascertainment bias, although the blinded-endpoint assessment is implemented specifically to mitigate interpretive bias. Second, the 12-week treatment window is sufficient for assessing short-term efficacy and safety but precludes conclusions about long-term outcomes, adherence, or sustained effects. In addition, the exclusion of patients with major depressive disorder may limit generalizability, given the high prevalence of depression in FM. We will partially address this by analyzing baseline Beck Depression Inventory-II in subgroup analyses. Finally, as no FM-specific dose-ranging data are available for crisugabalin, a formal dose-response analysis was not pre-specified, which represents a limitation of the study.

## Provenance and Peer Review

Not commissioned, externally peer reviewed.

## Study Status

Recruitment for this trial began in September 30, 2025. At the time of this manuscript's submission, the study is actively recruiting and has enrolled 100 participants. We estimate that the trial will need to continue for 3 years to reach the intended goal of 1116 participants. The trial is scheduled for completion in August 31, 2027.

## Abbreviations

FM, Fibromyalgia; PROBE, Prospective, randomized, open-label blinded-endpoint; NRS, Numerical rating scale; IMMPACT, Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials; AEs, Adverse events; ITT, Intention-to-treat; mITT, Modified intention-to-treat.

## Data Sharing Statement

This is the protocol only; no participant data are included.

## Patient Consent for Publication

Obtained.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This work was supported by the National Key Research and Development Program of China (No. 2022YFC3602200, No. 2022YFC3602201, No. 2022YFC3602202, No. 2022YFC3602203, No. 2022YFC3602205), the Capital's Funds for Health Improvement and Research (No. 2022-1-4061), and the National Health Commission Capacity Building and Continuing Education Center Cancer Pain Management (No. PMT1001-1). The sponsors were not involved in the trial design, trial conduct, data handling, data analysis, interpretation, manuscript preparation, or the decision to submit the article for publication.

## Disclosure

The authors declare no conflicts of interest in this work.

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