Randomized Trial

Analgesic Efficacy of Mirogabalin in Patients With Herpes Zoster: Protocol for a Prospective Multicenter Randomized Open-Label Blinded-Endpoint (PROBE) Study

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Background: Herpes zoster (HZ) is a debilitating condition characterized by acute dermatomal pain and a high risk of developing postherpetic neuralgia (PHN). Although early antiviral therapy is essential, its analgesic efficacy is often insufficient, particularly in patients with moderate to severe pain. While gabapentinoids are recommended as adjunctive analgesics, current options like gabapentin and pregabalin are often limited by inconsistent efficacy and dose-dependent adverse events. Mirogabalin, a novel gabapentinoid with higher affinity and selective dissociation for the $\alpha 2\delta$ subunit, may offer superior pain relief with a wider safety margin. However, although mirogabalin has demonstrated efficacy in PHN, its analgesic efficacy and safety in patients with acute HZ-associated pain have not been adequately established.

Objectives: To test the hypothesis that conventional treatment combined with mirogabalin provides superior pain relief compared to conventional treatment alone in patients with HZ.

Study Design: Multicenter, prospective, randomized, open-label, blinded-endpoint trial.

Setting: Beijing Tiantan Hospital, Second Hospital of Hebei Medical University, and Second Hospital of Shanxi Medical University.

Methods: A total of 750 adult patients experiencing moderate to severe pain with rash onset within the last 30 days will be enrolled. Patients will be randomly assigned in a 1:1 ratio to either mirogabalin group or control group. The mirogabalin group will receive oral mirogabalin in addition to conventional treatment, while the control group will receive conventional treatment alone. Mirogabalin will be titrated from 5 mg twice daily to a maximum of 15 mg twice daily according to individual tolerability and will be used during the prespecified treatment period up to 90 days after rash onset. After 90 days following rash onset, treatment will be identical in both groups, and patients with persistent pain meeting the definition of PHN will receive standardized guideline-based PHN management. The study duration will be 52 weeks. Patients and treating physicians will be aware of treatment allocation, whereas outcome assessors will remain blinded.

Results: The primary outcome is the average pain intensity at week 4. Secondary outcomes include the worst pain intensity, proportions of patients achieving $\geq$ 30% and $\geq$ 50% pain reduction, proportion of patients developing postherpetic neuralgia, type of analgesics and average weekly consumption per analgesics, the Herpes Zoster Severity of Illness Index, quality of life assessed by the 12-item Short Form Health Survey, sleep quality assessed by the Medical Outcomes Study Sleep Scale, the Neuropathic Pain Scale, and adverse events. These outcomes will be assessed at prespecified time points from baseline through week 52, according to the assessment schedule for each outcome. Statistical analyses will be performed based on the modified intention-to-treat population.

Limitations: The open-label design may introduce performance bias, although blinded endpoint assessment is intended to minimize this effect. Second, the findings may not be generalizable to patients with subacute HZ, PHN, or advanced chronic kidney disease.

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Conclusions: If mirogabalin combined with conventional treatment proves more effective and better tolerated than conventional treatment alone, it could establish a new evidence-based standard for optimizing pain management in patients with HZ.

Key words: Herpes zoster, mirogabalin, blinded-endpoint, postherpetic neuralgia

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Herpes zoster, commonly known as shingles, is a debilitating condition caused by the reactivation of the varicella-zoster virus latent in sensory ganglia following primary infection (1). Clinically, HZ is characterized by a unilateral, dermatomal, erythematous rash accompanied by vesicular eruption, crusting, and severe pain (1). Its prevalence increases significantly with age, affecting 7.7% of the general population and rising to 10.6% among individuals aged 70 years and older (2). The HZ-associated pain, marked by persistent or intermittent tingling, increased sensitivity, burning or sharp pain, and touch-induced discomfort, severely impacts patients' quality of life (3). The acute pain during HZ is not only distressing but also a risk factor for the development of postherpetic neuralgia (PHN), the most common complication of HZ (4,5). Approximately 29.8% of HZ patients develop PHN (2), a chronic neuropathic pain that can profoundly impair quality of life and impose significant psychological and functional burdens (3).

Current therapeutic strategies for HZ emphasize early antiviral intervention with agents such as famciclovir, valacyclovir, acyclovir, and brivudine to mitigate viral replication, accelerate cutaneous healing, minimize sensory nerve damage, and reduce the severity of pain (6,7). However, the analgesic efficacy of antiviral monotherapy remains suboptimal, particularly for moderate to severe pain, necessitating adjunctive analgesic approaches. European consensus guidelines advocate a stepwise analgesic regimen incorporating nonopioids (including nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, metamizole, etc.), mild opioids (such as tramadol) and strong opioids (including oxycodone, hydromorphone, etc.) based on pain intensity, though many patients still experience inadequate pain relief (1,7). This therapeutic gap underscores the need for alternative analgesic strategies to optimize pain management in HZ patients.

Gabapentinoids (gabapentin and pregabalin), structural analogues of γ-aminobutyric acid, exert their analgesic effects by binding to the $\alpha 2\delta$ subunit of voltage-dependent calcium channels, thereby reducing neurotransmitter release (8). This mechanism inhibits the central sensitization of dorsal horn neurons, providing pain relief (9). For the management of HZ with moderate to severe pain, both gabapentin and pregabalin are recommended as adjunctive analgesics by the European consensus-based guidelines and German guidelines for the management of HZ (7,10). A recent systematic review and meta-analysis supports the use of gabapentin, demonstrating a significant reduction in pain scores at 4 weeks compared to the placebo in HZ patients (11). However, this benefit comes at the cost of a higher risk of adverse events (AEs), including vertigo, drowsiness, dizziness, peripheral edema, which limit its clinical utility (11). Previous studies investigating the efficacy of pregabalin in managing HZ-associated pain have yielded mixed results. In a small-scale, randomized, double-blinded, placebo-controlled trial, a single dose of pregabalin demonstrated a trend toward greater reduction compared to placebo group (12). However, the study's limited sample size of only 8 patients precludes definitive conclusions, necessitating further exploration. Conversely, a prospective, randomized, double-blinded, placebo-controlled trial found no statistically significant benefit of pregabalin in alleviating acute HZ pain, with a statistically significant increase in the appearance of AEs (13). These conflicting findings underscore the limitations of current gabapentinoid use in acute HZ, characterized by inconsistent efficacy and tolerability issues.

Mirogabalin is a novel orally administered gabapentinoid approved in Japan for the treatment of peripheral neuropathic pain, including diabetic peripheral neuropathic pain and PHN (14).

Based on the above evidence, we hypothesize that conventional treatment combined with mirogabalin will provide superior pain relief compared to conventional treatment alone in patients with HZ, potentially with a more favorable AE profile. To rigorously evaluate the hypothesis, we propose a prospective, random-

ized, controlled, open-label, blinded-endpoint study to examine the analgesic efficacy of mirogabalin in patients with HZ.

Methods

Study Design

A multicenter, randomized, controlled, open-label, blinded-endpoint trial will be conducted to evaluate the analgesic efficacy of mirogabalin in patients with HZ. Patients with HZ will be enrolled from Beijing Tiantan Hospital, Second Hospital of Hebei Medical University, and Second Hospital of Shanxi Medical University from 2025 to 2027. The study was registered on www.clinicaltrials.gov (NCT07307170) on December 2025, and approved by the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University (KY2025-369-02), and other study center following the criteria required by the Helsinki Declaration. The flowchart is briefly illustrated in Fig. 1, and all trial procedures are summarized in Table 1.

Recruitment and Informed Consent

Patients diagnosed with HZ will be referred to experienced attending pain physician from the multicenter site. All candidates will undergo a rigorous evaluation to confirm their eligibility based on predefined inclusion and exclusion criteria. Willing patients who meet the eligibility criteria will be informed of the study objectives, interventions, potential benefits, and risks. Patients will be given sufficient time to review and address any questions they may have. Written informed consent will be obtained from patients or his/her legal surrogate. Patients understand that they may withdraw from the study at any time without any impact on their future medical care.

Study Population

Inclusion Criteria

1. Age 18 years or older
2. Patients with onset of HZ rash less than 30 days;
3. Experiencing moderate to severe HZ pain with an average pain score of at least 4 on a Numeric Rating Scale (NRS, 0 = no pain, 10 = worst possible pain);
4. Aspartate aminotransferase and alanine aminotransferase levels less than twice the upper limit of normal;
5. Estimated glomerular filtration rate of 30 mL/min per 1.73 m^2 or higher;
6. Willing to sign the informed consent form and pos-

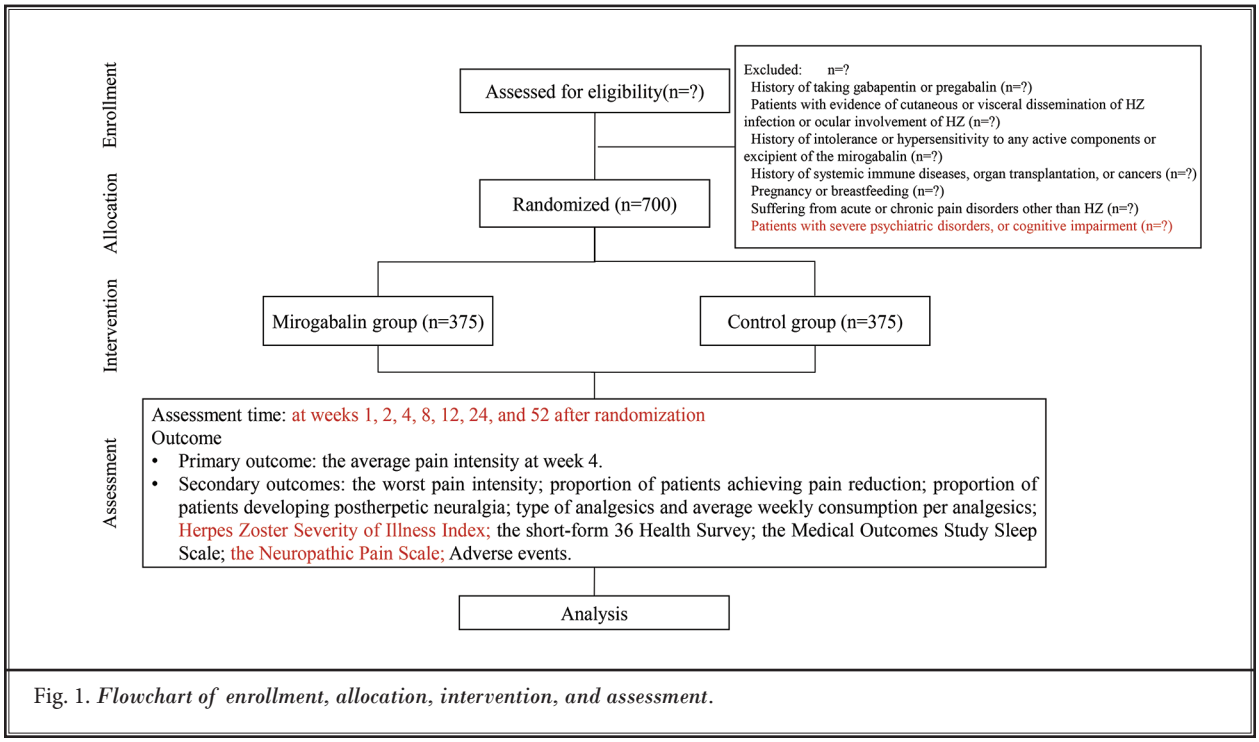


Fig. 1. *Flowchart of enrollment, allocation, intervention, and assessment.*

Table 1. *The schedule of enrollment, interventions, and assessments.*

	-1 day	0 day	1 week	2 weeks	4 weeks	8 weeks	12 weeks	24 weeks	52 weeks
Enrollment									
Eligibility screening	✓								
Informed consent	✓								
Allocation		✓							
Intervention									
Mirogabalin group		✓							
Control group		✓							
Assessment									
Baseline data	✓								
Mean pain intensity*					✓				
Worst pain intensity			✓	✓	✓	✓	✓	✓	✓
Proportion of responders achieving ≥ 30% and ≥ 50% reduction			✓	✓	✓	✓	✓	✓	✓
Proportion of patients developing postherpetic neuralgia							✓[a]	✓[a]	✓[a]
Type of analgesics and average weekly consumption per analgesics					✓	✓	✓	✓	✓
Herpes Zoster Severity of Illness Index					✓	✓	✓		
12-item Short-Form Health Survey					✓	✓	✓	✓	✓
Medical Outcomes Study Sleep Scale					✓	✓	✓	✓	✓
Neuropathic Pain Scale							✓[b]	✓[b]	✓[b]
Adverse events					✓	✓	✓	✓	✓

*Primary outcome.
✓ indicates the procedure or assessment is scheduled at the corresponding visit; blank cells indicate that it is not scheduled.
✓[a] Assessed only at visits occurring on or after 90 days following rash onset.
✓[b] Assessed only in patients who meet criteria for postherpetic neuralgia.

sessing sufficient cognitive and language abilities to comply with all the study requirements.

Exclusion Criteria

1. History of taking gabapentin or pregabalin;
2. Patients with evidence of cutaneous or visceral dissemination of HZ infection (cutaneous dissemination is defined as more than 20 discrete lesions outside adjacent dermatomes) or ocular involvement of HZ;
3. History of intolerance or hypersensitivity to any active components or excipient of the mirogabalin;
4. History of systemic immune diseases, organ transplantation, or cancers;
5. Pregnancy or breastfeeding;
6. Suffering from acute or chronic pain disorders other than HZ;
7. Patients with severe psychiatric disorders, or cognitive impairment.

Withdrawal Criteria

1. Non-compliance with the study protocol;
2. Occurrence of severe adverse events (SAEs) during the treatment period.

Randomization and Blinding

Patients who fulfill the eligibility criteria and complete informed consent will be randomly assigned to either the mirogabalin group or the control group in a 1:1 ratio. Randomization will be performed using an online software platform (www.sealedenvelope.com) with block size of 4. The randomization procedure will be managed by an independent research associate who has no access to study data and will not engage in patient interaction or collaborate with the research team. The allocation sequence list will be generated and stored securely on a central computer, inaccessible to investigators involved in the trial. To ensure allocation

concealment, sealed, opaque envelopes containing the randomization assignments will be prepared. The study is an open-label trial, so neither the researchers nor the patients will be blinded. The outcome assessors will not have knowledge of the administered intervention throughout data collection.

Procedures

Treatment Before 90 Days after Rash Onset

During the trial, patients will record their pain conditions in a pain diary every day. To minimize treatment heterogeneity and potential performance bias, conventional treatment will be standardized across both study arms according to prespecified protocol.

Antiviral therapy will be provided according to prespecified clinical indications (7). Patients who have not received antiviral treatment before enrollment and who still meet treatment indications will receive valacyclovir 1,000 mg orally 3 times daily to complete a 7-day course. Patients who have already initiated antiviral therapy before enrollment, including agents other than valacyclovir, will continue the original regimen to complete the recommended course. Detailed information on pre-enrollment antiviral exposure will be recorded.

Concomitant analgesic therapy will follow a protocolized stepwise regimen based on the 3-step World Health Organization pain ladder, guided by pain severity on the NRS (17). For mild pain defined as an NRS score of 3 or lower, first-line therapy will consist of nonopioid analgesics, such as NSAIDs. For moderate pain defined as an NRS score of 4 to 6, or for pain that persists despite optimized nonopioid therapy, escalation to a weak opioid in combination with a nonopioid analgesic will be permitted. For severe pain defined as an NRS score of 7 or higher, or for pain that remains inadequately controlled after the previous step, escalation to a strong opioid in combination with nonopioid analgesics will be allowed. To further standardize opioid use, dose escalation will be permitted only when prespecified criteria are met, including persistent inadequate analgesia despite the prior step or clinically significant breakthrough pain. Rescue medication will be restricted to protocol-specified short-acting analgesics and will be used only for breakthrough pain. For rescue treatment, patients may take 1,000 mg acetaminophen for mild breakthrough pain, with a maximum daily dose of 4,000 mg. For more severe breakthrough pain, oxycodone and acetaminophen combination tablets will be permitted, with each tablet containing 5 mg oxycodone hydrochloride and 325 mg acetaminophen, administered with a maximum of 4 times daily. All rescue medication use will be recorded in detail, including the agent, dose, frequency, and indication. Throughout the trial, procedural therapies, such as nerve blocks or pulsed radiofrequency, are forbidden.

In the mirogabalin group, patients will receive mirogabalin in addition to the same standardized conventional treatment used in the control group, including antiviral therapy, nonopioid analgesics, and opioid analgesics when clinically indicated. Mirogabalin (Mirogabalin Besylate, Daiichi Sankyo Co., Ltd., Japan) will be initiated at 5 mg twice daily. If the patient's NRS score reaches 0 within the first week, mirogabalin will be discontinued. Otherwise, the dose will be increased to 10 mg twice daily during the second week. If the NRS score reaches 0 within the second week, the dose will be reduced to 5 mg twice daily for 1 week and then discontinued. If pain persists, the dose will be further increased to 15 mg twice daily and maintained until an NRS score of 0 is achieved or until the 90 days after rash onset (18). After day 90 following rash onset, mirogabalin will be tapered and discontinued, with the dose reduced to 10 mg twice daily for approximately one week, followed by 5 mg twice daily for an additional week before discontinuation. With each dose increase, AEs will be assessed and categorized as mild, moderate, or severe. If patients tolerate the current dose, it will be maintained. If AEs become intolerable, the dose will be decreased back to the previous dose. If AEs are intolerable even at the initial dose, mirogabalin will be discontinued, and the patient will be withdrawn from the trial.

In the control group, patients will be treated with conventional treatment, identical to the conventional treatment of mirogabalin group.

Treatment At and After 90 Days Following Rash Onset

After 90 days from rash onset, treatment will be identical in both groups. Patients with persistent pain meeting the definition of PHN will receive standardized guideline-based PHN management, including gabapentinoids, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and topical agents such as lidocaine or capsaicin, as clinically appropriate (10). All PHN-related treatments and dose adjustments will be recorded in detail.

Follow-Up

The prospective trial protocol comprises 8 visits over 52 weeks (day 0 and weeks 1, 2, 4, 8, 12, 24, and 52).

Data Management and Quality Control

Study data will be captured by trained investigators using standardized Case Report Forms specifically developed for this protocol. To maintain high standards of data integrity and accuracy, all information will be recorded in a centralized electronic database (EpiData Manager, Version 4.6.0.6; EpiData Association, Denmark). A rigorous independent double-data entry protocol will be implemented. Discrepancies identified between the 2 entries will be verified and resolved by cross-checking against the original source documents.

An independent Data and Safety Monitoring Committee will be established to provide objective trial oversight. The committee will convene biannually to perform interim reviews of cumulative safety data and trial validity. Based on these evaluations and an assessment of the overall study conduct, the committee will offer formal recommendations to the Steering Committee regarding the continuation, modification, or potential early termination of the trial.

Patient and Public Involvement

Patients and the public were not directly involved in the conceptualization of the research question, the formulation of the study design, or the selection of clinical outcome measures. Patient recruitment will be conducted via physician referral at the participating multicenter clinical sites.

Following the completion of the study, findings will be disseminated to the global scientific community through presentations at international academic conferences and publication in peer-reviewed journals. Furthermore, a plain-language summary of the trial results will be made available to patients upon request following the final analysis.

Study Outcomes

Primary Outcome

The primary outcome is the average NRS score at week 4 after randomization.

Secondary Outcomes

1. The worst NRS score at week 1, 2, 4, 8, 12, 24, and 52 after randomization. It will be derived from the patients' pain diaries collected at the aforementioned follow-up time points.
2. Proportion of patients achieving pain reduction at week 1, 2, 4, 8, 12, 24, and 52 after randomization. The proportion of patients achieving a ≥ 50% and ≥ 30% reduction in mean baseline pain intensity.
3. Proportion of patients developing PHN, defined as persistent pain in the affected dermatome for at least 90 days after rash onset, with an average pain intensity of ≥3 on the NRS (20).
4. The type of analgesics and average weekly consumption per analgesics at week 4, 8, 12, 24, and 52 after randomization.
5. The Herpes Zoster Severity of Illness (HZSOI) Index (21,22) from rash onset to day 90. The HZSOI is a severity-by-duration measure of overall pain burden associated with HZ and is typically calculated as the area under the curve of the worst pain scores over a defined period after rash onset.
6. The 36-item Short-Form Health Survey (SF-36) (23) score at week 4, 8, 12, 24, and 52 after randomization. The SF-36 score assesses the health-related quality of life, capturing preferences across various health states. It assesses 8 dimensions: physical functioning, physical role limitations due to physical health, bodily pain, general health, vitality, social functioning, emotional role limitations due to emotional problems, and mental health. Scores range from 0 to 100 for each dimension, with higher scores indicating better health status.
7. The Medical Outcomes Study Sleep Scale (MOS) (24) at week 4, 8, 12, 24, and 52 after randomization. The MOS is a questionnaire comprising 12 items that assess various aspects of sleep using a 6-point ordinal scale (1 indicating permanence and 6 indicating absence).
8. Neuropathic Pain Scale (25) at or after 90 days following rash onset. Neuropathic pain characteristics will be assessed using the Neuropathic Pain Scale in patients with developing PHN. The Neuropathic Pain Scale consists of 10 numeric rating items, each scored from 0 to 10, with higher scores indicating greater neuropathic pain severity. The scale assesses pain intensity, unpleasantness, and 8 specific pain qualities, including sharp, hot, dull, cold, sensitive, itchy, deep, and surface pain.
9. AEs throughout the study. The incidence and proportion of AEs will be recorded and categorized as mild, moderate, severe, or life-threatening. AEs are defined as events that arise during treatment,

were absent before treatment, or worsen relative to the pretreatment state.

Statistical Analysis

Sample size calculation was performed using the PASS 11 software (NCSS, LLC, USA). In a systematic review and meta-analysis on efficacy and safety of gabapentin and pregabalin for acute HZ, findings suggested that patients who received gabapentin reported lower pain levels compared with the placebo group at 4 weeks (standardized mean difference = -2.79, 95% confidence interval = -4.71 to -0.88, $P = 0.004$) (11). However, there was no significant difference on pain scores treated with gabapentin and pregabalin at week 1 and 2, with standardized mean difference of -0.86 and -2.21, respectively. Based on this finding, we hypothesis that the average pain score of control group will be 5.0, and mirogabalin may reduce 10% pain score compared with control group. A sample size 674 patients (337 per group) is calculated to provide 90% power to detect the between-group difference, with an overall type I error of 0.05. To account for a dropout rate of 10%, the total required sample size is 750 patients (375 per group).

The final conclusion will be determined in line with the intention-to-treat principle in accordance with the CONSORT guideline. All analyses will be performed using both the modified intention-to-treat and per-protocol principles. All randomized patients will be included in the efficacy analyses if they have received at least one dose of the study medication, and have at least one post-baseline assessment of any efficacy parameter. For the safety population analysis, all randomized patients who receive at least one dose of the study medication will be included.

The primary outcome and other continuous variables will be described as mean ± standard deviation for normally distributed data or as median with interquartile range for non-normally distributed data, with normality assessed using the Shapiro-Wilk test. Between-group comparisons for normally distributed continuous variables will be performed using Student's t-test, whereas the Mann-Whitney U test will be applied for skewed continuous variables. Categorical variables will be expressed as counts and percentages and compared using the Chi-square test or Fisher's exact test, as appropriate. Repeated-measures data will be analyzed using repeated-measures analysis of variance or linear mixed-effects models, depending on data structure and distribution. All statistical tests will be 2-sided, and a P value < 0.05 will be considered statistically significant.

To address potential attrition, the missing data mechanism will be explored to determine if data are missing at random. Missing data for weekly pain intensity will be addressed using multiple imputation based on the Markov Chain Monte Carlo method. To evaluate the robustness of the primary outcome against different missing data assumptions, several sensitivity analyses will be conducted. In the worst-case scenario, patients who discontinued the study in the mirogabalin group will be assumed to have unfavorable outcomes, while dropouts in the control group will be assumed to have favorable outcomes. The inverse will apply in the best-case scenario. Baseline opioid exposure, antiviral treatment status at enrollment, and Somatic Symptom Scale-8 score will be included as a prespecified covariate in the primary efficacy analysis.

Furthermore, pre-specified subgroup analyses for the primary outcome will be performed based on age, gender, duration of HZ symptoms, and baseline pain intensity. A P value < 0.05 for the interaction term will be considered statistically significant to suggest a subgroup effect.

Discussion

This prospective, multicenter study is designed to evaluate the analgesic efficacy and safety of mirogabalin as an adjunctive therapy to conventional treatment for HZ pain. The primary objective is to determine if the superior pharmacological profile of mirogabalin translates into clinically significant pain reduction and improved tolerability for patients with HZ.

The PROBE design was selected to balance methodological rigor with clinical pragmatism. While a double-blind design is the gold standard, it can be restrictive in real-world titration scenarios. The PROBE approach mitigates potential assessment bias by ensuring that investigators responsible for outcome measurements remain blinded to group allocation, thereby strengthening the internal validity of the trial.

The primary outcome, the average NRS pain score at week 4, was chosen because the first month following rash onset is a critical window for intervention to prevent central sensitization. Rapid and effective pain control during this acute phase is not only essential for patient quality of life but is also considered a key factor in reducing the risk of transition to PHN.

Limitations

Several limitations of this study warrant consideration. First, the open-label nature of the intervention

may introduce performance or ascertainment bias, although the blinded-endpoint assessment is intended to counter this bias. Second, because the study enrolled only patients within 30 days after rash onset and excluded those with advanced chronic kidney disease, the findings may not be generalizable to patients with subacute HZ, PHN, or advanced chronic kidney disease, in whom gabapentinoids often require careful dose titration. Ultimately, the findings from this trial could significantly impact the clinical management of HZ. If mirogabalin proves to be a more effective and better-tolerated adjunctive analgesic than conventional therapy alone, it could establish a new evidence-based strategy for HZ pain.

Study Status

The first patient was enrolled in December 2025 after ethical approval was obtained. At the time of manuscript submission, the study was recruiting and 40 patients had been enrolled.

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