Journal of Pain Research

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STUDY PROTOCOL

Efficacy and Safety of SIKD1977 in Combination with Standard Treatment for Postherpetic Neuralgia: Study Protocol for a Double Blind, Placebo-Controlled, Randomized, Multicenter, Phase 2 Clinical Trial

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Purpose: Postherpetic neuralgia (PHN) is the most common chronic complication of herpes zoster, associated with poor quality of life and increased patient and healthcare resource expenditure. This randomized controlled trial aims to evaluate the efficacy and safety of SIKD1977 (Sogeonjungtang) in combination with standard treatment and estimate an effective dose for treating PHN.

Patients and Methods: This is a protocol for a randomized, placebo-controlled, double-blind, multicenter trial. A total of 90 eligible participants with PHN will be recruited from three hospitals and randomly allocated to high-dose group, low-dose group, or placebo group in a 1:1:1 ratio. The trial will involve a 6-week oral administration of SIKD1977/placebo, and a 1-week follow-up period. The primary outcome will be the weekly average change in average daily pain score (ADPS) from baseline to the end of treatment. The secondary outcomes will include the weekly average changes in ADPS from baseline to week 2, 4, and 7, differences in Short-Form McGill Pain Questionnaire, Visual analogue scale, 5-level EuroQol-5 dimensions, Patient Global Impression of Change, and consumption of rescue drugs. All adverse events will be assessed during the trial.

Conclusion: This study will provide evidence for the efficacy and safety of SIKD1977, and an effective dose for PHN.

Trial Registration: This protocol has been registered in the Clinical Research Information Service with the identification code KCT0007939.

Keywords: postherpetic neuralgia, herbal medicine, SIKD1977, Sogeonjungtang, randomized controlled trial, protocol

Introduction

Postherpetic neuralgia (PHN) is one of the intractable chronic pain syndromes, characterized by persistent pain for more than one month after the resolution of the herpes zoster rash.[1] Patients with PHN experience several types of pain: persistent pain without a stimulus (often described as burning, aching, throbbing), intermittent pain without a stimulus (often described as stabbing, shooting, or electric shock-like), and pain caused by a stimulus but is disproportionate to the stimulus.[2] In addition, it affects the quality of life by causing abnormal sensations (dysesthesias or paresthesias), depression, insomnia, and anorexia.[3]

Clinical guidelines for the management of PHN recommended tricyclic antidepressant (TCA), gabapentin, pregabalin, and topical lidocaine 5% patch as first-line therapies for patients with PHN. Although effective, TCAs have been

Received: 9 December 2022
Accepted: 10 May 2023
Published: 29 May 2023

associated with anticholinergic adverse events or cardiotoxicity, and calcium channels α2-δ ligands such as gabapentin and pregabalin have risks of dizziness, somnolence, peripheral edema, weight gain, asthenia, dry mouth, and vertigo.[4] In addition, topical lidocaine 5% patch may increase the incidence of adverse effects, such as blisters, bruising, burning sensation, dermatitis on the application site, confusion, disorientation, headache, and nervousness.[2]

Herbal medicine treatment has been used to treat a range of pain-related conditions, and several reviews have demonstrated that herbal medicine can be an effective treatment for patients with PHN.[5–7] Qua et al have found that herbal medicine groups significantly alleviated pain intensity compared to western medicine groups,[5] and Liang et al further have shown that herbal medicine as an add-on therapy to pharmacotherapy had a better effect in reducing pain intensity and depression symptom severity compared to pharmacotherapy alone.[6]

Paeoniae Radix and Glycyrrhizae Radix, which are the main herbs of Sogeonjungtang (SGJT), have already been used as a sedative, pain reliever, and anti-spasmodic in East Asia through anticholinergic, prostaglandin-production-inhibiting, antioxidation, and anti-inflammation as Jakyakgamchotang (also known as Shakuyakukanzo-to, Shaoyaogancao-tang).[8–11] In accordance with the study of Hidaka et al, Jakyakgamchotang could relieve pain in peripheral neuropathic pain-induced mice.[12] Furthermore, SGJT, which adds four components to this herbal medicine, reduces the intensity, time, and frequency of neuropathic pain in a retrospective observational study.[13] Thus, this clinical trial will assess the efficacy and safety of SIKD1977 (SGJT) in combination with standard treatment and confirm an effective dose for treating PHN.

Materials and Methods

Study Design and Setting

This study is a multicenter, randomized, placebo-controlled, double-blinded trial designed to evaluate the efficacy and safety of SIKD1977 combined with PHN standard treatment in patients with PHN. This trial will be performed at Dongguk University Bundang Oriental Hospital (Gyeonggi-do, Korea), Kyung hee University Hospital at Gangdong (Seoul, Korea), and Jaseng Hospital of Korean Medicine (Seoul, Korea). A total of 90 participants who meet the inclusion and exclusion criteria will be randomly divided into three groups in a 1:1:1 ratio: high-dose group, low-dose group, and placebo group. The trial will consist of a 6-week oral administration of SIKD1977/placebo and a 1-week follow-up period. The flow chart for this study is shown in Figure 1, and Table 1 shows the schedule for enrollment, intervention, and assessments.

Participants

Participants will be recruited through advertising posters approved by the Institutional Review Board (IRB). Recruitment posters will display inside and outside each hospital, such as on the subway and bus, and online.

Inclusion Criteria

The trial inclusion criteria are as follows:

1. Age of 19 to 65 years old.
2. Presence of persistent pain even after 1 month of PHN standard treatment (Pregabalin, Gabapentin).
3. Average numeric rating scale (NRS) for the past week ≥ 4.
4. Average daily pain score (ADPS) for the 1-week screening period ≥ 4.
5. Able to decide the participation, read, and write the informed consent (Those who demonstrate no problems with communication, both visual and auditory (reading, writing, hearing, speaking, and seeing)).
6. Voluntary willingness to participate and sign the informed consent agreement (Those who are not coerced or unduly influenced to engage in the research).

Exclusion Criteria

The exclusion criteria are as follows:

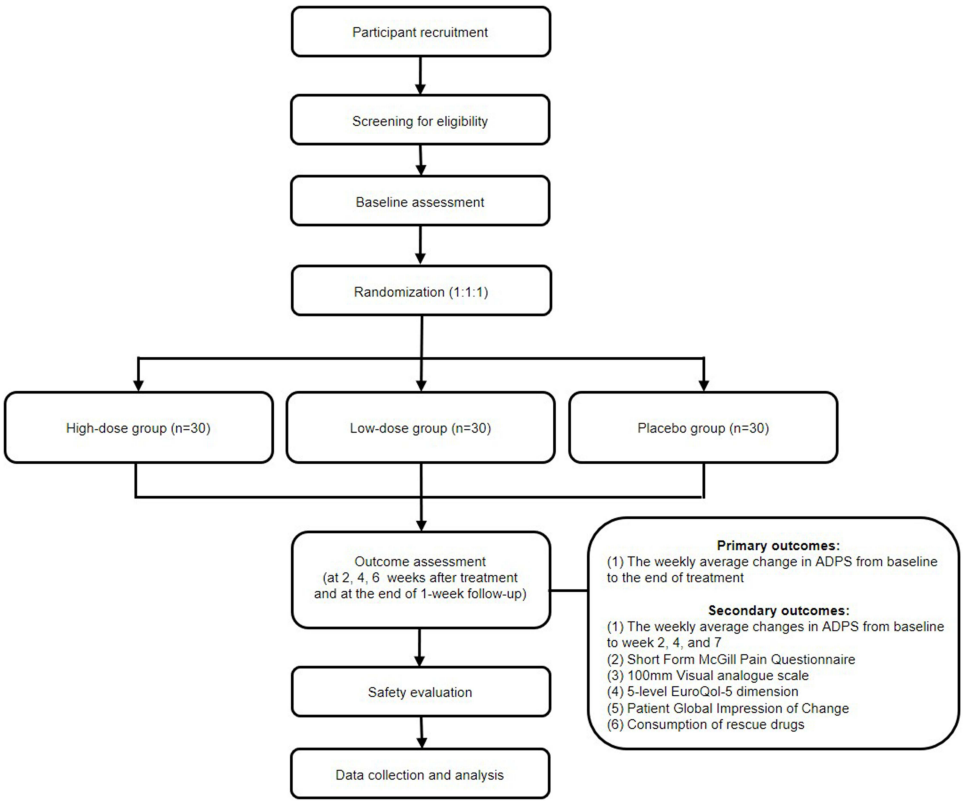

Figure 1 Study flow chart.
Abbreviation: ADPS, Average daily pain score.

1. Head and face affected by herpes zoster.
2. The recurrence of herpes zoster or the requirement for treatment:
3. Presence of severe nausea, vomiting, gastrointestinal diseases, or history of gastrointestinal surgery that may affect drug absorption.
4. Diabetic patient (fasting blood sugar ≥ 128mg/dL or HbA1c ≥ 6.5%); history of diabetes diagnosis or taking diabetes medication.
5. Presence or history of myopathy due to hypokalemia.
6. Presence of severe uncontrolled hypertension.
7. Presence or history of heart disease (coronary artery disease (eg cardiomyopathy, myocardial infarction, angina pectoris), congestive heart failure, asymptomatic cardiac dysfunction).
8. Presence of other severe pain, neurological diseases, or red flag sign unrelated to postherpetic neuralgia.
9. Presence of malignant cancer within the past five years, severe mental illness, or other systematic diseases.
10. Presence of the following abnormalities in laboratory tests: serum potassium <3.5mmol/L, creatinine clearance <30mL/min, or HBsAg/HCV Ab (+); abnormal findings in electrocardiogram.
11. Presence of hypersensitivity to components of SIKD1977; history of the allergic disease which needs to treat or drug allergy.
12. Use of the following drugs for postherpetic neuralgia: NSAIDs, corticosteroid, local anesthetic, opioid analgesics, antidepressants, muscle relaxant, immunosuppressant, potassium/licorice-containing agents, glycyrrhizic acid, thiazide diuretics, loop diuretics (However, participation is possible after washing out for more than 7 days (up to 4 weeks) in accordance with a half-life of each drug).
13. Those who have received or need the following therapy for treating postherpetic neuralgia: nerve block within the past 1 month, radiofrequency ablation, spinal cord stimulator insertion, implantation of a subarachnoidal drug administration system.

Table 1 Schedule of Enrolment, Treatments, and Assessments

	Screening	Baseline	Treatment Period			Follow-Up Period
		Week 0	Week 2	Week 4	Week 6	Week 7
Visit	1	2	3	4	5	6
Enrolment						
Informed consent	•					
Demographic characteristics	•					
Medical history	•					
Vital sign	•	•	•	•	•	•
Physical examination	•	•	•	•	•	•
Laboratory test	•	•			•	
Concomitant therapy	•	•	•	•	•	•
Concomitant medicine	•	•	•	•	•	•
Inclusion/exclusion criteria	•	•				
Randomization		•				
Intervention						
High-dose group			← 30g three times per day →			
Low-dose group			← 30g three times per day →			
Placebo group			← 30g three times per day →			
Assessment						
ADPS	•	•	•	•	•	•
NRS	•					
SF-MPQ		•	•	•	•	
100mm VAS		•	•	•	•	
EQ-5D-5L		•	•	•	•	
PGIC			•	•	•	
Drug consumption	•	•	•	•	•	
Adverse event	•	•	•	•	•	•

Abbreviations: ADPS, average daily pain score; EQ-5D-5L, 5-level EuroQol-5 dimension; NRS, numeric rating scale; PGIC, Patient Global Impression of Change; SF-MPQ, Short Form McGill Pain Questionnaire; VAS, visual analogue scale.

14. Use of herbal medication within the past 14 days; use of an over-the-counter drug (including vitamin B1 or B12) within the past 10 days.
15. Participation in other clinical trials within the past two months.
16. Disagreements with the use of the following contraceptive methods during the study period: intrauterine device, barrier contraceptives with spermicide, vasectomy, tubectomy, tubal ligation, or hysterectomy.
17. Females who are pregnant or lactating.
18. Other disqualifications as determined by the researcher.

Drop-Out Criteria

Participants may request cessation or withdrawal of participation in the study at any point in time, or the investigators may withdraw participants if they meet any of the following criteria.

1. Inclusion or exclusion criteria are violated.
2. Serious adverse events which make participation difficult.
3. Exacerbation of the disease requires to discontinue the study drug.
4. Self-administration of medications which affects the trial.

5. Participation in another clinical trial during this study.
6. A patient requests to withdraw consent.
7. A patient is pregnant.
8. Protocol violation which significantly affects the trial.
9. The researcher determines that further participation is inappropriate.

Randomization and Blinding

An independent statistician who is not involved in the clinical trial will perform randomization. It will be achieved with a computerized random number generator using the stratified block randomization method of SAS (SAS Institute, Inc., Cary, NC, USA). The random assignment will be done by the web-based service provided by the Interactive Web Response System (IWRS). A packer not related to this study will pack the study drug or placebo according to random codes of investigational products assigned through IWRS, and the pharmacist who does not participate in the study will provide the study drug or placebo with the same number as the random code.

The participants, investigators, clinical trial pharmacist, and other clinical trial associates will be blinded to the treatment assignment until the end of the study. Only when the study has been completed, the database query finished, and the study database locked will be the randomization schedule be made available for analysis.

If a serious adverse event cannot be managed without knowing what type of intervention has been received, the IWRS will be used to obtain treatment assignment information. The Medical Monitor must be notified before the study intervention is unblinded, preferably prior to unblinding a subject.

Intervention

Participants will receive high-dose SIKD1977, low-dose SIKD1977, or placebo three times per day according to group allocation. The duration of treatment in three groups is 6 weeks with a follow-up period of 1 week.

Samik Pharmaceutical Co. manufactures the SIKD1977 and placebo in compliance with Korea Good Manufacturing Practice standards. SIKD1977 (SGJT) used in this study is a sweet, dark brown, soft extract, and is permitted and regulated by the Ministry of Food and Drug Safety. It is composed of six components: *Paeoniae Radix Rubra* 0.5g, *Cinnamomi Ramulus* 0.33g, *Jujubae Fructus* 0.33g, *Glycyrrhizae Radix* 0.25g, *Zingiberis Rhizoma* 0.11g, *Saccharum Granorum* 1.67g (per 7.5g). The placebo has the appearance, shape, weight, taste, and color of the SIKD1977 being administered. SIKD1977 and placebo soft extract are sealed in aluminum bags and administered to subjects in doses of 7.5g. Participants will be instructed to take 30g of 4 packs per dose three times a day before meals. In the high-dose group and the placebo group, a total of 90g of SIKD1977 or placebo will be taken a day. In the low-dose group, two packs of SIKD1977 (15g) and two packs of placebo (15g) will be taken once together, and the daily dose was the same as 90g (SIKD1977 45g + placebo 45g) with the other two groups.

Concomitant Treatment

Pregabalin and gabapentin, which are PHN standard treatments, should be taken at least two weeks before trial and maintained under the same conditions during the clinical trial period.

If medications are needed to treat other diseases unrelated to pain, they can be taken during the trial period and should be taken at the same dosage and usage during the study.

Rescue Medication

If participants do not tolerate pain and want to take analgesics, acetaminophen will be permitted. Acetaminophen 500mg tablets should be taken once 1 ~ 2 tablets at intervals of 4 ~ 6 hours, and the maximum dose for 24 hours is limited to 4000mg. The participants will indicate the dosage, date of use in their diaries.

Outcome

Primary Outcome

The primary outcome measure will be the weekly average change in ADPS from baseline (visit 2) to the end of treatment (visit 5). The participants evaluated the average degree of pain within the previous 24 hours in the daily diary using NRS, which is defined as ADPS. The NRS ranges from 0 (no pain) to 10 (the worst imaginable pain) and is chosen to assess merely pain severity.

Secondary Outcome

The secondary outcomes of this trial are the weekly average changes in ADPS from baseline to week 2, week 4, and week 7, differences in Short-Form McGill Pain Questionnaire (SF-MPQ), Visual analogue scale (VAS), 5-level EuroQol-5 dimension (EQ-5D-5L), Patient Global Impression of Change (PGIC), and consumption of rescue drugs.

1. The weekly average changes in ADPS from baseline to week 2, 4, and 7
   Participants evaluated the average degree of pain over the past 24 hours in their diaries using NRS every day, and ADPS are checked and collected at each visit (Visit 2–6).
2. Short-Form McGill Pain Questionnaire (SF-MPQ)
   SF-MPQ is a shortened version of MPQ, consisting of 15 items of multidimensional scales, VAS, and present pain intensity. The 15 items of multidimensional scales (11 sensory; 4 affective) are rated on an intensity scale as 0 (no pain) to 3 (severe pain) for each question. The pain intensity over the past week will be assessed using VAS where one end of a 100mm line indicates no pain while the other end refers to the worst imaginable pain. The present pain intensity will be rated between 0 (no pain) to 5 (excruciating).[14,15] The participants will self-complete the SF-MPQ at visit 2–5.
3. 100mm Visual analogue scale (VAS)
   VAS included in the second category of SF-MPQ will be collected for evaluating pain over the past week.
4. 5-level EuroQol-5 dimension (EQ-5D-5L)
   EQ-5D-5L is a generic instrument for evaluating health-related quality of life. The descriptive system is composed of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five response categories corresponding to no problems, slight problems, moderate problems, severe problems, and extreme problems.[16] The participants will be asked to indicate their health state for each of the five dimensions at visit 2–5.
5. Patient Global Impression of Change (PGIC)
   PGIC, which has a consistent relationship with NRS changes regardless of study, disease type, age, sex, study result, or treatment group, is a self-reported tool for improvement levels using a 7-point scale (1: very much improved, 2: much improved, 3: minimally improved, 4: no change, 5: minimally worse. 6: much worse, 7: very much worse).[17] The PGIC will be administered during visits 3, 4, and 5.
6. Consumption of rescue drugs
   Whether or not the rescue drug is taken, the dosage and the duration of the drug are checked and collected through the participants' diaries at each visit.

Safety Evaluation

For safety evaluation, vital sign, weight, physical examination, concomitant treatment will be measured at every visit, and hematology tests (white blood cell, red blood cell, hemoglobin, hematocrit, platelet, differential count), urinalysis (specific gravity, color, pH, protein, glucose, ketone, bilirubin, occult blood, urobilinogen, microscopic examination), ECG will be conducted before and after treatment for three groups to compare the incidence of adverse events.

At each visit, the participants will report adverse events, and the investigator will record details, including the specific symptom, onset, duration, severity, resolution, and possible association with treatment. When serious adverse events occur, the investigator will suspend participation, provide the treatment immediately, and report to the IRB within 24 hours from the time of recognition regardless of causality.

Quality Control

Investigators will undergo adequate and professional training before the study and follow guidelines for Good Clinical Practice and Korean Good Clinical Practice, to ensure the safety of the subjects, and adherence to the protocol. To protect the rights and welfare of the subjects and to sustain the quality of the study, its own quality assurance process and monitoring will be conducted. The clinical research associate will regularly visit three centers or access the data management system to confirm the source document and monitor whether the trial is performed according to the protocol and related guidelines.

The study data will be collected and recorded in the electronic case report form (e-CRF). The study-related documents including consent forms, the CRF, questionnaires, medical records, and other records will be kept in a locked space or on a password-protected computer in each hospital for three years after study completion.

Sample Size Estimation

No previous clinical trials have evaluated the effect of SIKD1977 on patients with PHN. This study is a phase 2 trial designed to assess whether a treatment has a sufficient signal of the activity or other meaningful benefit to warrant further investigation in a definitive Phase 3 trial. Typically, the sample size of the phase 2 trial is small or moderate, ranging from tens to hundreds.[18] Teare et al suggested that pilot randomized controlled trials require a total of at least 70 for estimating a continuous outcome with good precision.[19] In addition, previous studies assessing the efficacy of herbal medicine as an add-on therapy for PHN set sample size from 30 to 35 per group.[20–24] Thus, considering the possibility of drop-outs and the other characteristics of this study, we have decided to recruit 30 participants per group.

Statistical Analysis

An independent statistician blinded to group allocation will perform both the full analysis set (FAS) and per-protocol (PP) analysis. FAS is performed on patients who take for study drug at least once, and missing data are replaced via the last observation carried forward method. PP analysis is used to evaluate data collected from the subjects, who complete all steps of the experimental protocol.

Data will be presented as the number of observations, mean, standard deviation, median, minimum, and maximum for continuous parameters, and the number, and percentage of subjects for categorical parameters. Comparison of the baseline characteristics will be analyzed by two-sample *t*-test or Wilcoxon's rank sum test for continuous variables, and Pearson's chi-square test or Fisher's exact test for categorical variables. For the primary outcome measure, we will implement analysis of covariance (ANCOVA) in which the dose of SIKD1977 (stratified variable) is a factor with standard treatment (pregabalin, gabapentin) considered as a covariate. For the secondary outcome measure, we will conduct ANCOVA in which each group (stratified variable) is a factor with standard treatment considered as a covariate. To analyze the percentage of patients taking the rescue drugs, we will perform the Cochran-Mantel-Haenszel test with standard treatment as a covariate.

To assess safety, we will present the frequency and proportions of adverse events, and we will use Pearson's chi-square test (or Fisher's exact test) to analyze differences among the three groups. We will conduct paired *t*-tests (or Wilcoxon's signed rank test) and McNemar's test using the results of the vital sign, physical examination, weight, laboratory tests, ECG of the baseline tests, and end of intervention tests, and we will estimate differences among the groups. In addition, concomitant medicines are classified according to the latest version of the World Health Organization-Anatomical Therapeutic Chemical index, and concomitant therapies are standardized to System Organ Class and Preferred Term according to the latest version of Medical Dictionary for Regulatory Activities, and the frequency and proportions of concomitant medicine/therapy are presented.

Ethics

All procedures in this trial will be conducted in compliance with general ethical guidelines (the Declaration of Helsinki and Korean Good Clinical Practices). This study was approved by IRB of Dongguk University Bundang Oriental Hospital (2022-D11-N001) and has been registered at Clinical Research Information Service (KCT0007939, https://cris.nih.go.kr/cris/search/detailSearch.do/23099).

The Ministry of Food and Drug Safety approved this clinical trial under the Investigational New Drug number 8WDT-VB8G-OL0M-BQZG on 19 May 2022.

Before enrolment, all participants will sign informed consent forms including possible benefits and adverse events, and their responsibilities. All enrolled subjects will voluntarily enter the study, and their personal information will be strictly protected under IRB supervision.

Discussion

PHN is the most common complication following herpes zoster, causing intractable chronic pain syndrome.[25] The first-line drugs, including calcium channel modulators, TCA, and lidocaine, are not suitable for long-term use and their efficacy is not completely reliable. Other treatments, such as opioid analgesics, tramadol, and topical capsaicin, have unclear long-term effects and safety.[26] Therefore, effective pain relief for PHN is a challenge for clinicians.

SGJT, also known as Shokenchu-to, Xiaojianzhong-tang, is described in a medical book called "Sang-Han-Lun" written in the 3rd century.[13] Previous studies have reported that SGJT has antioxidant, antidepressant, inhibitory of the immunoglobulin E dependent allergic reactions, anti-inflammatory, and immune response enhancement effects.[27–29] This herbal medicine is composed of six kinds of herbs: *Paeoniae Radix Rubra, Cinnamomi Ramulus, Jujubae Fructus, Glycyrrhizae Radix, Zingiberis Rhizoma*, and *Saccharum Granorum*. Paeoniflorin, a chief active ingredient in the root of *Paeoniae radix*, is effective in alleviating chronic neuralgia and promoting the repair of the damaged nerves by reducing the levels of inflammatory factors and Schwann cell apoptosis in rats with chronic sciatica.[30] Cinnamic acid, a standard compound from *Cinnamomi Ramulus,* has an effective analgesic action against oxaliplatin-induced neuropathic pain, especially in relieving cold and mechanical allodynia.[31] Glycyrrhizin, as one of the main active components of *Glycyrrhizae Radix*, was indicated to have anti-hyperalgesic effect in mice with diabetic peripheral neuropathy.[32] In addition, gingerol and shogaol had the effects of decreasing mechanical hypersensitivity and improving anxiety-like behavior in animal models, which showed that *Zingiberis Rhizoma* could have an important function in treating neuropathic pain.[33] These experimental evidence support that SGJT could have important clinical functions in treating PHN.

Previous randomized controlled trials of SGJT have significantly affected digestive diseases such as chronic atrophic gastritis, peptic ulcer, constipation-predominant irritable bowel syndrome, and there are only observational studies in other fields, including nocturnal enuresis and heartburn.[34–37] Previously, there have been severe studies for SGJT, but clinical trials using it for pain reduction have been scarce. Therefore, this study conducting a randomized controlled trial to assess the effectiveness and safety of SGJT for relieving neuropathic pain, will be highly meaningful.

Gabapentin and pregabalin, used as PHN standard treatments in this study, act on the α2-δ subunit of the calcium ion channel with an analgesic action on neuropathic pain.[38] These are first-line drugs for treating PHN in the guidelines in Europe and the United States.[39–42] Gabapentin and pregabalin have no serious complications compared with other anticonvulsants or antidepressants.[43] In addition, these are considered attractive options for older patients who take several concomitant medications because they have a low propensity for drug interactions with co-administered drugs, not metabolized by cytochrome P450 system drug-metabolizing enzymes.[2,44] Therefore, we designed these medications as suitable standard treatment for those who will be co-administered with study drugs.

In a review regarding herbal medicine for PNH, patients who received herbal medicine with western medicine for four weeks obtained a significant improvement in pain intensity relief than those who received less than four weeks. This suggests that a longer duration of treatment is required to attain meaningful pain relief in PHN treatment.[6] Based on this result, this study will be conducted for six weeks.

To our knowledge, this is the first study to investigate the efficacy of SIKD1977 with standard treatments for PHN patients, as a randomized, placebo-controlled, double-blind, multicenter trial. The study will ascertain whether using SIKD1977 with standard treatment for PHN can relieve pain intensity, improve quality of life, and reduce the use of analgesic medicine. These findings will help clinicians to utilize SIKD1977 with standard treatment as a therapeutic option for patients with PHN.

Abbreviations

ADPS, average daily pain score; ANCOVA, analysis of covariance; e-CRF, electronic case report form; EQ-5D-5L, 5-level EuroQol-5 dimension; FAS, full analysis set; IRB, Institutional Review Board; IWRS, Interactive Web Response System; NRS, numeric rating scale; GIC, Patient Global Impression of Change; PHN, postherpetic neuralgia; PP, per-protocol; SF-MPQ, Short-Form McGill Pain Questionnaire; SGJT, Sogeonjungtang; TCA, tricyclic antidepressant; VAS, visual analogue scale.

Trial Status

The final protocol version is 2.2, dated 26 September 2022. The recruitment will begin on 1 February 2023. We anticipate that it would be take 2 years to complete this trial.

Data Sharing Statement

Data and material from this trial are available upon reasonable request and approved by the corresponding author.

Author Contributions

Hyo-Rim Jo is the first author. 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; have agreed on the journal to which the article has been submitted; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. And they will also accept the responsibility for the study protocol.

Funding

This research is supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health & Welfare, Republic of Korea (grant number HF22C0071). The funding source has no role in the design of the study, collection, analysis, and interpretation of data, and in writing the manuscript.

Disclosure

Yong-Gyun Kim and Young-Ee Kwon are employees of Samik Pharmaceutical Company, the sponsor of this study. None of the other authors were financially compensated for their collaboration in this project or for the development of this paper. The authors report no other conflicts of interest in this work.

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