Study Protocol

Mirogabalin treatment of postoperative neuropathic pain after thoracic surgery: study protocol for a multicenter, randomized, open-label, parallel-group, interventional trial

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Background: Intercostal nerve damage due to thoracotomy or thoracoscopic manipulation is a major contributor to chronic postsurgical pain after pulmonary resection. Chronic postsurgical pain may last for months or years and can negatively impair physical functioning and daily activities. Global consensus on severe postoperative pain management is lacking, and chronic pain incidence after thoracic surgery remains high. Many patients report neuropathic pain, which can be difficult to treat with currently available therapies. The efficacy and safety of mirogabalin have been demonstrated for other types of neuropathic pain; thus, this study was planned to investigate the efficacy and safety of mirogabalin to treat neuropathic pain after thoracic surgery.

Methods: In this multicenter, randomized, open-label, parallel-group, interventional study, patients who are diagnosed with neuropathic pain following removal of a chest drain after lung resection will receive conventional therapy (non-steroidal anti-inflammatory drugs and/or acetaminophen) with or without the addition of a clinical dose of mirogabalin for 8 weeks. For patient stratification, a visual analog scale pain intensity score at baseline of <60 *vs.* ≥60 mm will be used. Treatment efficacy and safety with and without the addition of mirogabalin will be assessed using a questionnaire evaluating postoperative changes in pain severity and activity. The primary study endpoint is the change in pain intensity from baseline to Week 8, measured by the visual analog scale. Additionally, the presence of chronic pain at 12 weeks after enrollment in each treatment group will be recorded.

Discussion: This protocol has been reviewed and approved by the Clinical Research Review Board of Nagasaki University. Study data will be published in the Japan Registry of Clinical Trials database and peer-reviewed journals. Mirogabalin is already approved for the treatment of other types of neuropathic pain. It is anticipated that this study will provide data to elucidate the impact of mirogabalin treatment, in combination with conventional therapy, to benefit patients with neuropathic pain following thoracic surgery.

Trial Registration: Japan Registry of Clinical Trials Identifier: jRCTs071200053.

Keywords: Mirogabalin; postoperative neuropathic pain; thoracic surgery; postthoracotomy pain syndrome

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Introduction

One of the most common reasons for visiting a hospital in the US is chronic pain (1-3). It is estimated that about 22.5% of cases involve pain that arises after surgery (4). Chronic postsurgical pain (CPSP) is defined as pain that continues for ≥3 months following the surgical procedure (5,6). In a meta-analysis, the incidence of chronic pain at 3 and 6 months after thoracic surgery was found to be 57% and 47%, respectively (7). For some patients, CPSP may last many months or even years (8). Even mild pain, if it is persistent and chronic in nature, can impair physical function and reduce physical and social activities (9). Neuropathic pain is defined as pain resulting directly from a lesion or disease affecting the somatosensory system either at the peripheral or central level (10). Roughly a third of patients who develop CPSP after thoracic surgery present a neuropathic pain component, which has been associated with more marked physical dysfunction, as well as worse quality of life, than CPSP without the neuropathic component (11).

Intercostal nerve damage due to thoracotomy or thoracoscopic manipulation is a major contributor to CPSP after pulmonary resection (12), with variations in incidence depending on the types of surgical procedures and manipulations performed (13,14). In a retrospective analysis of thoracic surgery in Japan, 10/14 patients (71.4%) who converted from minimally invasive video-assisted thoracoscopic surgery to invasive thoracotomy reported postoperative neuropathic pain. Of these, three patients developed intractable symptoms (15). In a second retrospective analysis of 200 Italian patients who underwent lung resection via minithoracotomy or video-assisted thoracoscopic surgery, the overall incidence of CPSP was 35%. Additionally, pain with a neuropathic component occurred at an incidence of 16% in women and 6% in men (16). A numeric rating scale ranging from 0–10 can be used in clinical settings to assess the severity of chronic pain related to thoracic surgery (17). Studies using this reliable and validated measure suggest that pain control during the acute postoperative phase and for up to 3 months following surgery is critical for reducing CPSP (17). However, despite the high rate of chronic pain development after thoracic surgery (11,18), optimal pain treatments during the first 3 postoperative months have not been established.

Current treatments for pain control after thoracic surgery include local anesthetics (epidural anesthesia, paravertebral body block, intercostal nerve block), which are commonly administered in the perioperative period (19). Oral anti-inflammatory analgesics [e.g., non-steroidal anti-inflammatory drugs (NSAIDs) and/or acetaminophen] can also be administered postoperatively and have been shown to be beneficial in postoperative surgical patients without contraindications (20). For severe postoperative pain, treatments vary by region, and consensus on a global management protocol is lacking. In Japan, antiepileptic drugs or oral agents to treat neuropathic pain may be prescribed (21); elsewhere, narcotic agents or multidisciplinary management techniques are recommended (22). Recommended first-line drugs for the treatment of neuropathic pain include tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors (e.g., duloxetine), and gabapentinoids (e.g., gabapentin and pregabalin) (23,24). However, clinical outcomes have varied; pregabalin has shown some effectiveness in reducing pain after thoracic surgery (25,26) but lacked efficacy during the critical early postoperative stage (27). Overall, despite treatment, it is clear that chronic pain incidence after thoracic surgery remains high.

Mirogabalin besilate (hereinafter referred to as mirogabalin) is approved in Japan as a treatment for peripheral neuropathic pain (28,29), and provides analgesic effects via binding to the $\alpha_2\delta$ subunit of voltage-gated calcium channels (30). The efficacy and safety of mirogabalin have been demonstrated for other types of neuropathic pain, such as diabetic peripheral neuropathic pain (31-33) and postherpetic neuralgia (34,35). Mirogabalin has not yet been assessed in patients with thoracic postsurgical pain, in whom the incidence of neuropathic pain is also high. However, it is anticipated that mirogabalin treatment will benefit patients with neuropathic pain following thoracic surgery.

We present the following article in accordance with the SPIRIT reporting checklist (available at https://dx.doi.org/10.21037/jtd-21-741).

Research purpose

The study is being conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Clinical Research Review Board of Nagasaki University (approval number CRB7180001), and informed consent will be obtained from all individual participants.

This study was planned to investigate the efficacy and

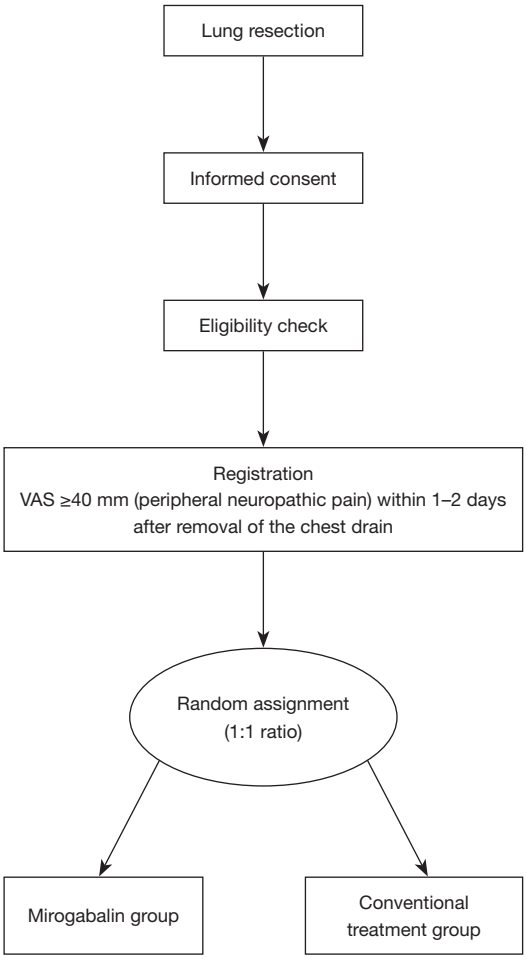

Figure 1 Study flow. Patients assigned to the conventional treatment group received conventional pain medications (non-steroidal anti-inflammatory drugs and/or acetaminophen). Patients assigned to the mirogabalin group received conventional treatment plus mirogabalin. VAS, visual analog scale.

safety of mirogabalin, in combination with conventional therapy, in treating neuropathic pain after thoracic surgery. As a chest tube insertion has deleterious effects on intercostal nerve function (14), patients who undergo lung resection will receive a clinical dose of mirogabalin in addition to conventional therapy for 8 weeks if they are diagnosed with neuropathic pain after the removal of the chest drain. This will be applied regardless of the type of surgical resection. Treatment efficacy and safety with and without the addition of mirogabalin will be assessed based on the results of a questionnaire evaluating postoperative changes in pain severity and activity. In addition, the presence of chronic pain at 12 weeks after enrollment in each treatment group will be recorded.

The study is registered at the Japan Registry of Clinical Trials (jRCT) with the identifier jRCTs071200053.

Study details

Study design and ethical considerations

This is a multicenter, randomized, open-label, parallel-group, interventional study. Participation of patients from at least 14 medical institutions is planned (Table S1), and a schematic of the study flow is provided in *Figure 1*. The enrollment period began in December 2020 and will remain open until December 2021; the observation period will run from December 2020 to March 2022.

The study is being conducted in accordance with the Declaration of Helsinki (revised October 2013) and the Clinical Research Act (promulgated April 14, 2017). In addition, all applicable local, national, and international legislation will be applied. The study protocol and associated documentation have been reviewed and approved by the Clinical Research Review Board of Nagasaki University (approval number CRB7180001), and permission to conduct the study was obtained from the administrators of each participating medical organization. The protocol is designated TLG-DS-19009 (version 3.0; dated March 25, 2021).

Participant selection

In principle, all patients undergoing lung resection at the participating medical institutions will be screened for study eligibility, with application of the detailed inclusion and exclusion criteria following the surgical procedure to identify patients with neuropathic postoperative pain suitable for study participation.

The inclusion criteria are as follows: patients undergoing lung resection (for any medical condition) who were aged ≥20 years at the time of informed consent; study enrollment was possible within 1–2 days after removal of the chest drain at the time of pulmonary resection; a visual analog scale (VAS) score of ≥40 mm (range 0–100 mm where 0 mm is no pain and 100 mm is worst pain) for perioperative pain at rest at the time of enrollment; hypoesthesia under the innervation of the intercostal space at the wound site (to exclude postoperative pain mainly caused by nociceptive

pain and to restrict eligibility to neuropathic pain) and no residual effect of epidural anesthesia at enrollment. All patients are required to provide written informed consent (documented by the study investigator) prior to study participation.

To ensure that patients with peripheral neuropathy after thoracic surgery are correctly and consistently diagnosed, neuropathic pain will be evaluated using a neuropathic pain diagnostic algorithm for subjective symptoms that includes a questionnaire and a pin-prick sensation test as an objective assessment of symptoms based on the grading system developed by the International Association for the Study of Pain Special Interest Group on Neuropathic Pain (36). The test for loss of pin-prick sensation will be performed at registration. In brief, patients will be placed supine with their eyes closed and normal sensation outside the site of surgery will be tested using a toothpick. It will be confirmed that there are no effects due to anesthesia (if anesthesia is determined to affect the results, the test will be repeated at a later time point). Next, hypoesthesia at the surgical wound site will be determined; the presence of hypoesthesia is taken to indicate neuropathy.

The exclusion criteria include total pleuropulmonary resection or pleurectomy; history of previous thoracotomy or thoracoscopic surgery resulting in neuropathy which continued until the time of the current surgery (and which would confound the identification of neuropathy resulting from the most recent surgery); serious liver dysfunction at enrollment; creatinine clearance (Cockcroft-Gault equation) <30 mL/min in the 3 months prior to enrollment; use of medications for neuropathic pain between 1 month before surgery and the time of enrollment; receipt of neoadjuvant chemotherapy within 2 months before surgery (to exclude chemotherapy-related neuropathic pain); hypersensitivity to any study treatment; pregnancy or lactation; presence of severe pain outside the perioperative wound area complicating the assessment of efficacy in this study; and any patient deemed inappropriate for participation in the study by the investigator or who might be endangered by study participation. If any patients were to require adjuvant chemotherapy with cisplatin, such patients would be discontinued from the study.

The concomitant use of several therapies will be prohibited during the study period. These therapies include pregabalin and gabapentin, duloxetine, tramadol, platinum chemotherapy agents, probenecid and cimetidine, and lorazepam. Postoperative nerve block, surgical procedures, or any other intervention (e.g., electrical stimulation, radiation therapy) that may affect the evaluation of treatment effectiveness will also be prohibited.

Randomization and interventions

Eligible patients will be randomly assigned to one of two treatment groups by the registration system, using a permuted block method (ratio 1:1). The stratification factors used in this study will be a VAS score of <60 *vs.* ≥60 mm at baseline and study site.

In the conventional treatment group, NSAIDs and/or acetaminophen will be prescribed per usual practice and in accordance with the package insert (including on-demand use) and insurance coverage. Patients are required to maintain a stable treatment regimen during the study. If the given medication does not adequately control pain, the investigator will consider prescribing medications that are not listed among the prohibited concomitant medications. For patients in the conventional treatment group, the investigator will consider increasing the dose of concomitant drugs to treat pain if needed to achieve pain control. Nevertheless, patient pain control will prevail as per ethical standards. If patients require prohibited concomitant medications to manage their pain, they will be discontinued from the study.

In the mirogabalin treatment group, in addition to conventional treatment, patients will also receive mirogabalin for 8 weeks. The dosage will be adjusted according to creatinine clearance, in line with the package insert. For patients with creatinine clearance ≥60 mL/min, the mirogabalin dose administered will be 5 mg twice daily (BID) during Week 1, 10 mg BID during Week 2, and 15 mg BID thereafter. Additional adjustments are allowed for tolerability, between 10–15 mg BID. For patients with creatinine clearance ≥30 and <60 mL/min, the mirogabalin dose administered will be 2.5 mg BID during Week 1, 5 mg BID during Week 2, and 7.5 mg BID thereafter. Additional adjustments are allowed for tolerability, between 5–7.5 mg BID. In cases where mirogabalin is discontinued, caution should be taken, and a gradual taper implemented. Patients who discontinue mirogabalin within 8 weeks from the start of treatment will be discontinued from the study.

Measures and endpoints

The study schedule is shown in *Table 1*. Data on baseline patient, surgical, and treatment characteristics will be collected. Additionally, the following items will be

Table 1 Investigation, observation, examination, and administration schedule

Procedure	Informed consent	Registration	Treatment period					End of study	Discontinuation
Visit	–	1	2	3	4	5	6	7	–
Week	–	0	0	0	2	4	8	12	–
Day	–	0	1	3	14	28	56	84	–
Visit window (days)	–	–	–	–	8–21	22–35	50–63	78–91	X–6–X+7
Informed consent	○[†]								
Eligibility check		○							
Study treatment		←	—	—	—	—	→		
Surgical information obtained		○							
Status of study drug administration		○	●	●[‡]	●	●	●		
Concomitant and prohibited medication check		○	●	●[‡]	●	●	●	●	●
VAS pain intensity (at rest and with cough)		○	●	●[‡]	●	●	●		●[#]
VAS sleep disturbance		○	●	●[‡]	●	●	●		●[#]
LANSS		○			●	●	●		●[#]
PDAS		○					●		●[#]
EQ-5D-5L		○					●		●[#]
PGIC							●		●[#]
Chronic pain							●	●	●[§]
Patient diary provided							●		
Patient diary checked								●	●[§]
Discontinuation information									●
Adverse events		←	—	—	—	—	—	—	→

○ indicates items to be performed before the start of study treatment, and ● indicates items to be performed after the start of study treatment. [†], informed consent will be obtained between the time of lung resection and the time of enrollment; [‡], Visit 3 should be performed as far as possible; [#], to be performed only if discontinuation occurs before Visit 6; [§], to be performed only if discontinuation occurs after Visit 6. Double-ended arrows indicates the duration of the study treatment and monitoring of adverse events. EQ-5D-5L, EuroQol 5-dimension 5-level measure; LANSS, Leeds Assessment of Neuropathic Symptoms and Signs; PDAS, Pain Disability Assessment Scale; PGIC, Patient Global Impression of Change; VAS, visual analog scale.

measured during the observational period: pain intensity (using VAS at rest and while coughing); sleep disturbance (using VAS); Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) score (37); Pain Disability Assessment Scale (PDAS) score (38); EuroQol 5-dimension 5-level (EQ-5D-5L) score (39); Patient Global Impression of Change (PGIC) (40); and adverse events (AEs) and adverse drug reactions elicited during physician interviews with patients. Treatment completion rates will be measured at study completion. In the case of AE onset, the investigator will assess each case individually and consider whether the patient should continue treatment at a maintained or reduced dose or if the patient should be discontinued from the study.

The primary study endpoint is the change in pain intensity from baseline to Week 8, measured by VAS. Secondary endpoints are the proportion of patients with improvements of ≥30% and ≥50% from baseline at Week 8 in pain intensity (using VAS at rest); the percentage of patients with a LANSS score of ≥12 at Weeks 2, 4, and 8; the change from baseline on various assessment scales, including VAS at rest (Day 1, Weeks 2 and 4), VAS while

coughing (Day 1, Weeks 2, 4, and 8), PDAS (Week 8), EQ-5D-5L (Week 8), VAS for sleep disturbance (Day 1, Weeks 2, 4, and 8), and PGIC (Week 8); and the prevalence of chronic pain at Weeks 8 and 12 in each treatment group.

Sample size and statistical analyses

With reference to a previous clinical study of pregabalin for postthoracotomy pain (26), the mean difference in change in VAS after 8 weeks between the conventional treatment group and the mirogabalin group was estimated to be 13.2 [standard deviation (SD) 22.5]. Thus, the number of patients needed to ensure 90% power at a two-sided 5% significance level would be 126 (63 patients per treatment group). Accounting for possible dropouts, the target sample size was set at 150 patients (i.e., 75 per group).

Baseline data for each treatment group will be summarized; categorical values will be summarized as frequency and percentage, and quantitative values will be summarized as the number of subjects, mean, SD, minimum value, median value, and maximum value.

Primary efficacy analyses will be performed using a modified intent-to-treat (mITT) population, defined as all randomized patients who received at least one dose of the study drug. A linear mixed model for repeated measures (MMRM) will be applied to the primary endpoint data. Adjusted estimates of mean differences at Week 8 (mirogabalin combination group minus conventional treatment group) with their 95% confidence intervals and P values will be calculated. MMRM will include treatment group (mirogabalin, conventional treatment), time points (Day 1, Weeks 2, 4, and 8), and treatment-by-time interaction as fixed effects, VAS at enrollment (baseline) as covariates, and patient as a random effect. Summary statistics will be calculated for each time point and change from baseline by treatment group. For the secondary endpoints, frequency tables or summary statistics will be reported for the mITT population.

Sensitivity analyses will be performed using a per-protocol set, defined as all mITT patients who adhered to the study protocol. For the primary endpoint, VAS measurements at Week 8 will be imputed using the last observation carried forward method. Using analysis of covariance with baseline VAS as covariates, estimates of differences in adjusted means of VAS change from baseline to Week 8 (mirogabalin group minus conventional group) with their 95% confidence intervals and P values will be calculated. The same analysis will be performed when data handling is imputed using the baseline observation carried forward method.

Safety will be assessed in all enrolled patients who received at least one dose of the study drug. AEs will be coded using the medical dictionary for regulatory activities (MedDRA) version 23.1 or later. To calculate the completion rate for 8 weeks after thoracic surgery, the number of patients receiving the effective dose at Week 8 will be divided by the number of patients at the start of the initial dose (Week 1).

Statistical analyses will be performed using SAS version 9.4 or later (SAS Institute, Inc., Cary, NC, USA) and Microsoft Excel 2016 or later (Microsoft Corp., Redmond, WA, USA).

Data management and study dissemination

Patient information will be collected and stored in accordance with the Act on the Protection of Personal Information (Act No. 57 of 2003) and related notices. Appropriate anonymization will be applied. An electronic data capture system (CubeCDMS; CRScube APAC KK, Tokyo, Japan) will be used for data collation.

This research will be conducted in accordance with the Clinical Research Act (including the Enforcement Regulations of the Clinical Research Act and related notifications) and the protocol, and the study will be monitored by an independent Clinical Research Organization according to prespecified procedures and processes. Auditors will conduct document-based conformity investigation and field investigation independent of monitoring and ensure the reliability of research conduct and record-keeping. The investigators and participating medical organizations will facilitate the access of source documents to monitors and auditors when requested.

The sponsor, Daiichi Sankyo Co., Ltd., will provide the necessary funding for the conduct of this study and will be involved in designing the study plan, the data management plan, and the statistical analysis plan, in collecting safety information, and in overseeing the study and communicating important protocol modifications. However, the sponsor will not be directly involved in monitoring, data management, statistical analysis, or data auditing. All authors will have access to the final dataset. Study data will be published in the jRCT database and peer-reviewed journals.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the SPIRIT reporting checklist. Available at https://dx.doi.org/10.21037/jtd-21-741

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study is being conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Clinical Research Review Board of Nagasaki University (approval number CRB7180001), and informed consent will be obtained from all individual participants.

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