CLINICAL STUDY PROTOCOL

AMELA study

-An Asian, multicenter, randomized, double-blind, placebo-controlled 14-week study of mirogabalin in patients with central neuropathic pain followed by a 52-week open-label extension-

-For Double-Blind Phase-

DS5565-A-J314

VERSION 1.0, 18 SEP 2018
VERSION 1.1, 22 OCT 2018
VERSION 2.0, 11 JAN 2019
VERSION 2.1, 10 FEB 2020
VERSION 2.2, 30 SEP 2020

DAIICHI SANKYO

INVESTIGATOR AGREEMENT

AN ASIAN, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED 14-WEEK STUDY OF MIROGABALIN IN PATIENTS WITH CENTRAL NEUROPATHIC PAIN FOLLOWED BY A 52-WEEK OPEN-LABEL EXTENSION

Sponsor Approval:

This clinical study protocol has been reviewed and approved by the Daiichi Sankyo representative listed below.

Print Name	**Signature**
Title	**Date (DD MMM YYYY)**

Investigator's Signature:

I have fully discussed the objectives of this study and the contents of this protocol with the Sponsor's representative.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Council for Harmonisation guidelines on Good Clinical Practice (ICH E6), and applicable regional regulatory requirements.

I agree to make available to Sponsor personnel, their representatives and relevant regulatory authorities, my subjects' study records in order to verify the data that I have entered into the case report forms. I am aware of my responsibilities as a Principal Investigator as provided by the Sponsor.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the Sponsor.

Print Name	**Signature**
Title	**Date (DD MMM YYYY)**

PROTOCOL SYNOPSIS

EudraCT:	Not Applicable
IND Number:	Not Applicable
Protocol Number:	DS5565-A-J314
Investigational Product:	mirogabalin
Active Ingredient(s)/INN:	[(1*R*,5*S*,6*S*)-6-(Aminomethyl)-3-ethylbicyclo[3.2.0]hept-3-en-6-yl] acetic acid monobenzenesulfonate
Study Title:	An Asian, multicenter, randomized, double-blind, placebo-controlled 14-week study of mirogabalin in patients with central neuropathic pain followed by a 52-week open-label extension
Study Phase:	Phase 3
Indication Under Investigation:	Central Neuropathic Pain (CNeP)
Study Objectives:	Primary Objective • To compare change from baseline in the weekly average daily pain score (ADPS) at Week 14 in patients with CNeP after spinal cord injury (SCI) receiving mirogabalin versus placebo. Secondary Objective • To compare the ADPS responder rate at Week 14 (proportion of subjects with ≥ 30% and ≥ 50% reduction in ADPS from baseline at Week 14) between mirogabalin and placebo • To evaluate the effect of mirogabalin on additional pain questionnaires, including Short-Form McGill Pain Questionnaire (SF-MPQ), and the Neuropathic Pain Symptom Inventory (NPSI), • To assess the effect of mirogabalin on quality of life (QOL), activities of daily living (ADL), mood and sleep, patient impressions in pain, and allodynia • To characterize the safety and tolerability of mirogabalin based on body weight, adverse event (AE), clinical laboratory values, vital sign, 12-lead electrocardiogram (ECG), medical interview, Columbia-Suicide Severity Rating Scale (C-SSRS),

	Hospital Anxiety and Depression Scale (HADS), and edema.
Estimand:	Estimand in this study is the mean difference mirogabalin vs. placebo for change from baseline in weekly ADPS at Week 14 in patients with moderate and over chronic CNeP due to traumatic SCI. The missing weekly ADPS due to study treatment discontinuation will be imputed as if the subjects continue the study up to Week 14 without any study treatment after the discontinuation.
Study Design:	Multinational, randomized, double-blind, placebo-controlled, parallel-group study The planned study duration for each subject will be approximately 16 weeks, consisting of 1-week observation period, 14-week treatment period and 1-week follow-up period after last dose. After completion of the observation period, the eligible subjects will be randomized into one of the mirogabalin-arm or placebo-arm at the ratio of 1:1, with stratification factors of baseline ADPS (< 6.0 or ≥ 6.0) and region (Japan and the others).
Planned Study Duration:	First patient enrolled: Mar 2019 Last patient last visit (including follow-up): Jan 2021
Study Sites and Location:	Approximately 120 sites in Japan, Korea, and Taiwan
Subject Eligibility Criteria:	Inclusion Criteria: Subjects must satisfy all of the following criteria to be included. 1. Age ≥ 20 years at informed consent 2. Able to give informed consent for the study participation, understand procedures of this study, and complete patient-reported questionnaires adequately 3. Spinal cord injury due to trauma (eg, turnover, fall, traffic accident, sports accident) 4. C4-T12 spinal cord injury identified on MRI 5. American Spinal Injury Association (ASIA) impairment scale A, B, C, or D 6. Neuropathic pain region expressed at level and/or below level of spinal cord injury 7. ≥ 6 months after SCI at screening

8. Stable CNePSCI at least for 3 months prior to screening
9. At screening, a pain scale of ≥ 40 mm on Visual Analog Scale (VAS) of SF-MPQ
10. At randomization, a pain scale of ≥ 40 mm on VAS of SF-MPQ, and completion of at least 4 days of daily pain diaries with an ADPS of ≥ 4 over the past 7 days on the 11-point Numerical Rating Scale (NRS)

Exclusion Criteria:

Subjects who meet any of the following criteria to be excluded from participation in the study.

1. On any one day during the observation period, pain score of 10 on a scale of 0 (no pain) to 10 (worst possible pain)
2. Other severe pain at screening or randomization, unrelated to CNePSCI, that may confound the assessment of CNePSCI
3. Neurologic disorders at screening or randomization, unrelated to CNePSCI, that may confound the assessment of CNePSCI
4. Major psychiatric disorders within 1 year prior to screening
5. Patient who has secondary-gain from CNePSCI (eg, legal dispute, settlement negotiations) at screening or randomization
6. Spinal cord injury due to suicidal behavior
7. Patient who blames the third party for his/her spinal cord injury, in the case of spinal cord injury due to the third party act (Those patients can rarely overcome the pain due to the psychiatric factor)
8. Previous administration of pregabalin ≥ 300 mg/day for subjects with creatinine clearance (CLcr: using the Cockcroft-Gault equation) ≥ 60 mL/min or pregabalin ≥ 150 mg/day for subjects with CLcr 30 to < 60 mL/min for at least 4 weeks, declared lack of effect
9. Previous administration of gabapentin ≥ 1200 mg/day for subjects with CLcr ≥ 60 mL/min or gabapentin ≥ 600 mg/day for subjects with CLcr

30 to < 60, for at least 4 weeks, declared lack of effect

10. Use of mirogabalin, pregabalin, or gabapentin within 28 days prior to screening
11. Use of strong opioids for analgesic of CNePSCI within 3 months prior to screening
12. CLcr (using the Cockcroft-Gault equation) < 30 mL/min at screening
13. Malignancy other than basal cell carcinoma within the past 2 years prior to screening
14. Clinically significant unstable endocrine (eg, diabetes mellitus), neurologic, ophthalmologic, hepatobiliary, respiratory, hematologic illness, or cardiovascular disease (eg, uncontrolled cardiac arrhythmia, or myocardial infarction) at screening or randomization
15. Clinically significant findings on ECG at screening
16. History of pernicious anemia, untreated hypothyroidism, or human immunodeficiency virus infection
17. Pregnancy, potential pregnancy, breast feeding, or subject unwilling to take reliable contraceptive measures during the study or for 4 weeks after study completion
18. Known hypersensitivity to mirogabalin, pregabalin, or gabapentin
19. Participation in another clinical study, either currently or within 30 days prior to providing of informed consent
20. Experience of participating mirogabalin clinical study and receiving investigational product
21. Abuse of illicit drugs or alcohol history
22. Response of "yes" to any of the questions on the C-SSRS at screening or randomization in relation to events occurring within the past 12 months
23. At screening, clinical laboratory values exceeding limits listed in Table 4.1

	24. The subject who is considered inappropriate for the study at the discretion of the investigator or sub-investigator
Dosage Form, Dose and Route of Administration:	One tablet of either mirogabalin or matching placebo will be administered orally twice daily (BID) (in the morning and at bedtime). In mirogabalin group, patients with CLcr ≥ 60 mL/min at screening, will start with 5 mg BID of mirogabalin at first week, followed by 10 mg BID at second week as titration phase. From the third week, if there are no problems in safety, the patients will escalate the dose to 15 mg BID. For the following visits, the dosage may be changed to either 10 mg BID or 15 mg BID depending on safety findings at the time of each visit. Patients in placebo group take matching placebo throughout the entire period. In mirogabalin group, patients with CLcr 30 to < 60 mL/min at screening, will start 2.5 mg BID of mirogabalin at first week, followed by 5 mg BID at second week as titration phase. From the third week, if there are no problems in safety, the patients will escalate the dose to 7.5 mg BID. For the following visits, the dosage may be changed to either 5 mg BID or 7.5 mg BID depending on safety findings at the time of each visit. Patients in placebo group take matching placebo throughout the entire period.
Study Endpoints:	Primary efficacy endpoint: • Change from baseline in the weekly ADPS at Week 14 Secondary efficacy endpoints: • ADPS Responder rate defined as the proportion of subjects with ≥ 30%, and ≥ 50% reduction from baseline to Week 14 • Change from baseline in parameters assessed using the SF-MPQ • Patient Global Impression of Change (PGIC) • Change from baseline in parameters assessed using the NPSI • Change from baseline in average daily sleep interference score (ADSIS) • Change from baseline in Medical Outcomes Study (MOS) sleep scales • Change from baseline in the HADS

	• Changes from baseline in parameters assessed using Five Level EQ-5D version (EQ-5D-5L) • Changes from baseline in parameters assessed using Spinal Cord Independence Measure (SCIM) III • Change from baseline of allodynia
Planned Sample Size:	A total of 274 patients will be randomized to one of the placebo-arm or mirogabalin-arm at the ratio of 1:1.
Statistical Analyses:	Efficacy: Modified intent-to-treat (mITT) analysis set will be used as a primary for all efficacy analyses. Mean change from baseline in the weekly ADPS at Week 14 will be compared between mirogabalin arm and placebo using the following multiple imputation (MI) method and analysis of covariance (ANCOVA). The primary imputation will be based on "nonfuture dependence" model using the pattern mixture approach with shifting parameters under the missing not at random (MNAR) mechanism for the missing weekly ADPS data. Reason for dropout together with the time of dropout will be used for constructing the missing data pattern. The statistical model used for the MI data generation will be the Markov Chain Monte Carlo (MCMC) method with adjustment for relevant covariates to produce a monotone pattern first, and then the imputation will continue using the Regression with Predictive Mean Matching (REGPMM) method for the monotone pattern with the same set of covariates. Each complete imputed dataset will be analyzed using the ANCOVA with treatment as the fixed effects, and baseline ADPS as the covariate. The results of ANCOVA analysis from each complete imputed dataset will be combined using Rubin's rule. All reasons for discontinuation will be categorized, to the extent possible, into either lack of efficacy (LOE) or AE based on detail specified in the case report form (CRF). Only reasons that cannot be classified into the above two categories will be considered as "any other reasons (AOR)." The primary shifting parameter values corresponding to the three categories in the pattern mixture model (PMM) will be chosen as (1.0, 1.0, 0.5) for dropouts due to AE, LOE and AOR, respectively, and the corresponding shifting amount of the weekly ADPS

imputed at first missing week is given by (1.0, 1.0, 0.5)*residual standard deviation (RSD)*U(0,1) where U(0,1) is a random variable from a uniform distribution with a range of 0 to 1, and RSD is the RSD at first missing week after imputation.

Sensitivity analysis for the primary endpoint includes the followings:

- The primary analysis on the mITT analysis set using "nonfuture dependence" MNAR model with different shift parameters including (3, 3, 1.5), (5, 5, 2.5), and (0, 0, 0).

Supplementary analysis for the primary endpoint includes the followings:

- The primary analysis on the mITT analysis set using placebo multiple imputation
- ANCOVA with baseline ADPS and treatment as covariates on the mITT analysis set using baseline observation carried forward
- ANCOVA with baseline ADPS and treatment as covariates on the mITT analysis set using last observation carried forward
- The primary analysis on the PPS using "nonfuture dependence" MNAR model with the shift parameters of (1, 1, 0.5).

Response rate, defined as the proportion of subjects with ≥ 30%, and ≥ 50% reduction from baseline in ADPS at Week 14**,** will be compared between each mirogabalin arm and placebo, using logistic regression model.

Safety:

The treatment-emergent AEs, clinical laboratory tests results, vital signs, body weight, 12-lead ECG, evaluation of edema, C-SSRS, and HADS will be summarized using the safety analysis set.

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ADL	activities of daily living
ADPS	average daily pain score
ADR	adverse drug reaction
ADSIS	average daily sleep interference score
AE	adverse event
A/G ratio	albumin/globulin ratio
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AOR	any other reasons
ASIA	American Spinal Injury Association
AST	aspartate aminotransferase
BID	twice daily
BUN	blood urea nitrogen
CNeP	central neuropathic pain
CNePSCI	CNeP after SCI
CNS	central nervous system
CLcr	creatinine clearance
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
C-SSRS	Columbia-Suicide Severity Rating Scale
DPNP	diabetic peripheral neuropathic pain
eCRF	electronic case report form
EC	Independent Ethics Committee
ECG	electrocardiogram
EDC	electronic data capture
EIU	exposure in utero
EMA	European Medicines Agency
EQ-5D-5L	Five Level EQ-5D version
ESRD	end stage renal disease

ABBREVIATION	DEFINITION
GCP	Good Clinical Practice (refers to ICH and Code of Federal Regulations)
γ-GT (γ-GTP)	gamma-glutamyl transpeptidase
GOT	glutamic oxaloacetic transaminase
GPT	glutamic pyruvic transaminase
HADS	Hospital Anxiety and Depression Scale
ICF	informed consent form
ICH	International Council for Harmonisation
INN	International Nonproprietary Names
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISFLB	independent sub-functional lead of biostatistics
ISNCSCI	International Standards for Neurological Classification of Spinal Cord Injury
LDH	Lactate Dehydrogenase
LOE	lack of efficacy
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
mITT	modified intent-to-treat
MMRM	mixed effects model for repeated measurements
MNAR	missing not at random
MOS	Medical Outcomes Study
NeP	Neuropathic pain
NPSI	Neuropathic Pain Symptom Inventory
NRS	Numerical Rating Scale
OAB-SS	Overactive Bladder Symptom Score
PGIC	Patient Global Impression of Change
PHN	post-herpetic neuralgia
PK	pharmacokinetic(s)
PMM	pattern mixture model
PNeP	peripheral neuropathic pain
PPS	per-protocol set

ABBREVIATION	DEFINITION
PT	Preferred term
QD	once daily
QOL	quality of life
RBC	red blood cell
REGPMM	Regression with Predictive Mean Matching
RSD	residual standard deviation
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System
SCI	spinal cord injury
SCIM	Spinal Cord Independence Measure
SD	standard deviation
SF-MPQ	Short-Form McGill Pain Questionnaire
SOC	system organ class
T-Bil	total bilirubin
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VAS	Visual Analog Scale
WBC	white blood cell

1. INTRODUCTION

1.1. Background

Neuropathic pain is defined as pain initiated or caused by a lesion or dysfunction in the nervous system. Neuropathic pain has a variety of causes, including diabetes mellitus, viral infection, and spinal cord injury. Typical symptoms are spontaneous pain, hyperalgesia, and allodynia. The severity and duration of these symptoms vary greatly, depending on the etiology of the condition.[1] Findings from research in animal models suggest a relationship between the induction of neural lesions and changes in the level of ion channel and receptor expression in the cell membrane (cell membrane remodeling).[2] Those findings indicate that cell membrane remodeling lowers the action potential threshold and causes abnormal heterotopic firing among primary neurons and dorsal root ganglions. This in turn elicits the symptoms of neuropathic pain (NeP).[1,3] However, the relationship remains unclear between cell membrane remodeling and the lesions that cause this remodeling. This lack of clarity contributes to difficulties in the formulation of treatment plans and in the selection of therapeutic drugs.

Because a wide variety of pathologies can contribute to NeP, the patient population is extremely diverse.[3,4,5] Neuropathic pain can be treated with agents such as anticonvulsants (including α2δ ligands and carbamazepine), tricyclic antidepressants, and serotonin/norepinephrine reuptake inhibitors. Combination drug therapy is the usual form of treatment; mono-therapy is insufficient for effect.[5,6,7,8] The mechanisms of action are well-known for the drugs for treatment of this condition. Existing assessment methods can be used to estimate the mechanism of pain onset and continuation, based on the extent of pain relief that is provided by each drug. Unfortunately, however, these drugs do not provide adequate pain relief in many cases. In addition, all of these drugs are associated with adverse drug reactions (ADRs) that are related to the central nervous system (CNS). The question of tolerability is thus important for many patients, and especially for patients who receive combination drug therapy.[5,8] Because of insufficient drug efficacy and the prevalence of ADRs, considerable unmet need remains in this therapeutic area.

Gabapentin and pregabalin, which are commercially available α2δ ligands, are associated with fewer problems related to tolerability and drug interactions than other available drugs.[5] The α2δ ligand bind to the α2δ subunits of voltage-dependent Ca^{2+} channels that are expressed in nerve cell membranes. The α2δ ligand is thought to relieve pain through the inhibition of abnormal neural transmissions, primarily in the posterior horn of the spinal cord.[9,10,11,12] The mechanism of action is not completely understood. However, in animal models of NeP, research findings indicate that the α2δ ligand reduces calcium flow through voltage-dependent Ca^{2+} channels and inhibits the release of excitatory neurotransmitters such as glutaminic acid, norepinephrine, and substance P.[9,10,11,12] Gabapentin and pregabalin are currently considered first-line drugs for NeP in Europe and the United States. However, the dose is limited for both drugs because of the incidence of significant ADRs at high dose levels. As a result, these drugs do not provide adequate pain relief in many cases. The most common ADRs are dizziness and

somnolence, but weight gain and peripheral edema can also be of clinical importance.[13] Greater efficacy and safety are still needed in this class of drugs.

1.2. Study Rationale

1.2.1. Description of Investigational Drug

Mirogabalin binds with high affinity to the α2δ subunit of voltage-dependent Ca^{2+} channels. The α2δ subunit is expressed in the neural synapses, and analgesic action appears to be elicited when mirogabalin binds to this subunit.

Nonclinical studies (see Section 1.2.2) and clinical studies for diabetic peripheral neuropathic pain (DPNP) and post-herpetic neuralgia (PHN) (see Section 1.2.3) indicate that mirogabalin is strongly expected to be useful in the treatment of NeP, including patients with renal impairment.

1.2.2. Nonclinical Studies

Evidence from nonclinical studies suggests that NeP symptoms may be due to changes in the protein content of membranes of injured neurons ("membrane remodeling"). This process can lower the threshold for action potential generation, resulting in abnormal and spontaneous firing in peripheral and primary afferent and dorsal root ganglionic neurons. Treatment with an α2δ ligand is reported to reduce the calcium ion (Ca^{2+}) influx through voltage-dependent Ca^{2+} channels, and therefore to reduce the subsequent release of excitatory neurotransmitters such as glutamate, norepinephrine, and substance P.[9,10,11,12]

In nonclinical experiments, mirogabalin showed potent and highly specific binding affinity to the α2δ subunit. Mirogabalin also demonstrated a stronger analgesic effect than pregabalin in rodent models of peripheral neuropathic pain (PNeP). In spinal cord injury model rats, single oral administration of mirogabalin (2.5, 5, and 10 mg/kg) significantly increased the pain threshold. The increase in the pain threshold was still significant 8 hours after administration of either 2.5 mg/kg or 10 mg/kg. Additional information on nonclinical studies can be found in the Investigator's Brochure.

1.2.3. Clinical Experience

The efficacy, safety, and tolerability of mirogabalin were evaluated in 20 Phase 1 studies, 2 Phase 2 studies, 8 Phase 3 studies. In this section, pivotal two Phase 3 studies in patients with DPNP and PHN, the study in patients DPNP and PHN with renal impairment, and clinical pharmacology studies in subjects with renal impairment are shown.

1.2.3.1. Phase 3 Study in Patients With Diabetic Peripheral Neuropathic Pain

This was a multi-center, randomized, double-blind, placebo-controlled, 14 week study of mirogabalin in Asian subjects with DPNP followed by a 52-week open label extension (DS5565-A-J303). This study was conducted in Japan, Korea, Taiwan and Malaysia. The patients with creatinine clearance (CLcr) < 60 mL/min were excluded.

1.2.3.1.1. Double-blind Phase of the Study

In this phase, mirogabalin was administered at doses of 15 mg once daily (QD), 10 mg twice daily (BID), or 15 mg BID for 14 weeks, including the titration period, to evaluate the efficacy and safety of mirogabalin in Asian patients with DPNP. The mean ADPS at Week 14 decreased from baseline in all treatment groups. The 10-mg BID group and 15-mg BID group showed improvement in ADPS compared with the placebo group, and the differences versus placebo were statistically significant in the 15-mg BID group. The results of some secondary efficacy endpoints showed the efficacy of mirogabalin (especially 10 mg BID and 15 mg BID) with statistically significant differences compared with placebo. Although, in the primary efficacy endpoint, the 10 mg BID group did not show a statistically significant difference compared with the placebo group, the results of the primary and secondary efficacy endpoints suggested the efficacy of 10 mg BID of mirogabalin. Therefore, mirogabalin 15 mg BID is considered effective, and the efficacy of 10 mg BID is also suggested.

Overall, the incidence of treatment-emergent adverse events (TEAEs) and the most common TEAEs of nasopharyngitis, somnolence, dizziness, and weight increased were higher as the daily dose of mirogabalin was increased; and the vast majority of these events were mild. Two deaths were reported, but were considered unrelated to the study drug. No specific safety concerns in other reported serious TEAEs, or otherwise, were found. Therefore, mirogabalin 15 mg QD, 10 mg BID, and 15 mg BID are considered well tolerated in patients with DPNP.

1.2.3.1.2. Open Label Extension Phase of the Study

In this phase, mirogabalin was administered in a flexible dosage of 10 mg BID and 15 mg BID for 52 weeks in Asian subjects with DPNP, including the titration period, to evaluate the safety and efficacy of mirogabalin in patients with DPNP.

In terms of safety, the incidence of TEAEs leading to treatment discontinuation was low. The most common TEAEs were similar to those in the DB study and no increased risks with a long term administration of mirogabalin were observed in this study. The results indicated that mirogabalin administered in a flexible dosage of 10 mg BID and 15 mg BID for up to 52 weeks in subjects with DPNP was well tolerated.

In terms of efficacy, certain improvement of SF-MPQ subscales (sensory score, affective score, total score, VAS, and present pain intensity) was observed throughout the treatment period compared to the baseline. Mirogabalin administered in a flexible dosage of 10 mg BID and 15 mg BID for up to 52 weeks indicated a long-term efficacy of mirogabalin in pain relief in subjects with DPNP.

1.2.3.2. Phase 3 Study in Patients With Post-Herpetic Neuralgia

This was a multi-center, randomized, double-blind, placebo-controlled, 14 week study of mirogabalin in Asian subjects with PHN followed by a 52-week open label extension (DS5565-A-J304). This study was conducted in Japan, Korea, Taiwan, Singapore, Malaysia, and Thailand. The patients with CLcr < 60 mL/min were excluded.

1.2.3.2.1. Double-Blind Phase of the Study

In this phase, mirogabalin was administered at doses of 15 mg QD, 10 mg BID, or 15 mg BID for 14 weeks in Asian subjects with PHN, including the titration period, to evaluate the efficacy and safety of DS-5565 in patients with PHN. The mean ADPS at Week 14 decreased from baseline in all treatment groups. The efficacy of 10 mg BID and 15 mg BID of mirogabalin was superior to placebo in the change in ADPS from baseline at Week 14. The efficacy of 15 mg QD of mirogabalin was also superior to placebo in the change in ADPS from baseline at Week 14. The results of secondary efficacy endpoints also showed trends consistent with the result of the primary efficacy endpoint and supported the results of the primary analysis. It is considered that mirogabalin administered at doses of 15 mg QD, 10 mg BID, or 15 mg BID in patients with PHN is effective.

Overall, the incidence of TEAEs and the most common TEAEs of somnolence, dizziness, and edema were higher as the daily dose of mirogabalin was increased, and the vast majority of these events were mild. No deaths were reported, and no specific safety concerns in other reported serious TEAEs, or otherwise, were found. No other specific safety concerns were found. Therefore, mirogabalin 15 mg QD, 10 mg BID, and 15 mg BID are considered well tolerated in patients with PHN.

In conclusion, mirogabalin 15 mg QD, 10 mg BID, and 15 mg BID are considered efficacious, and well tolerated in patients with PHN.

1.2.3.2.2. Open Label Extension Phase of the Study

In this phase, mirogabalin was administered in a flexible dosage of 10 mg BID and 15 mg BID for up to 52 weeks in Asian subjects with PHN, including the titration period, to evaluate the long-term safety and efficacy of mirogabalin in patients with PHN.

In terms of safety, the incidence of TEAEs leading to treatment discontinuation was low. The most common TEAEs were similar to those in the DB study and no increased risks with a long term administration of mirogabalin were observed in this study. The results indicated that mirogabalin administered in a flexible dosage of 10 mg BID and 15 mg BID for up to 52 weeks in subjects with PHN was well tolerated.

In terms of efficacy, certain improvement of SF-MPQ subscales (sensory score, affective score, total score, VAS, and present pain intensity) was observed throughout the treatment period compared to the baseline. Mirogabalin administered in a flexible dosage of 10 mg BID and 15 mg BID for up to 52 weeks indicated a long-term efficacy of mirogabalin in pain relief in subjects with PHN.

1.2.3.3. Study for DPNP or PHN Patients With Renal Impairment

This was an open-label 14-week study for treatment of DPNP or PHN in subjects with moderate or severe renal impairment in Japan. Mirogabalin was administered at doses of 7.5 mg BID for subject with CLcr 30 to < 60 mL/min, and at dose of 7.5 mg QD for subjects with CLcr 15 to < 30 mL/min, including the titration period, to evaluate the safety of mirogabalin in patients with renal impairment. In terms of safety, the incidence of TEAEs were similar to those being observed in the pivotal Phase 3 studies in patients

with DPNP and PHN, and specific concerns for patients with renal impairment were not observed. In efficacy, change in ADPS from baseline at week-14 were almost same as the changes of 15 mg BID in the 2 Phase 3 studies described in Section 1.2.3.1 and Section 1.2.3.2, regardless of the degree of renal impairment.

1.2.3.4. Clinical Pharmacology Studies in Subjects With Renal Impairment

A clinical pharmacology study was conducted to assess PK of mirogabalin in Japanese subjects with renal impairment. In this study, following administration of single oral doses of 5 mg mirogabalin to healthy subjects, subjects with mild (50 to $\leq$ 80 mL/min/1.73 m^2), moderate (30 to < 50 mL/min/1.73 m^2), or severe renal impairment (< 30 mL/min/1.73 m^2), and subjects with end stage renal disease (ESRD), the overall exposure to mirogabalin, based on AUC, increased with severity of renal impairment. As assessed using the geometric least squares mean ratios, exposure was approximately 1.3, 1.9, 3.6, and 5.3 fold greater for subjects with mild, moderate, and severe renal impairment and ESRD, respectively, compared to subjects with normal renal function. Apparent clearance and renal clearance of A200-0700 decreased with increasing severity of renal impairment.

1.2.4. Study Rationale

In the two phase 3 studies in patients with DPNP and PHN which are different etiologies, pain improvement of mirogabalin was proved and degree of the improvement showed similar dose response in DPNP and PHN. In addition, exogenous and endogenous factors except for renal function are considered to have a little effect on efficacy of mirogabalin, as a result of pooled analysis of two phase 3 studies. Therefore, mirogabalin is expected to be useful in the treatment of PNeP. Nonclinical study in using rat with spinal cord injury as the typical experimental central neuropathic pain (CNeP) model indicated that mirogabalin single dose significantly improved mechanical allodynia of the rat, and time course and effective dose of analgesic effect in the CNeP rat model are similar those of analgesic effect in PNeP rat model. PNeP and CNeP have a common pathology that both pain are caused by a lesion or dysfunction of nerve system. In fact, clinical studies of pregabalin, which has the same mechanism of action of mirogabalin, in patients for PNeP and CNeP showed same efficacy profile. These results suggest that mirogabalin is expected to have same efficacy profile in patients with CNeP as PNeP. CNeP after spinal cord injury (SCI) (CNePSCI) is mentioned as major CNeP. Therefore, in this study, CNePSCI is selected as target disease.

1.2.5. Risks and Benefits for the Study Subjects

Anticipated risks of mirogabalin include the occurrence of adverse reactions related to CNS depression, such as dizziness and somnolence, peripheral edema, weight gain, loss of consciousness, ophthalmologic disorders, abrupt or rapid discontinuation, as well as glucose intolerance. Other notable TEAEs that have been observed in conducted clinical studies include elevations of hepatic transaminases and suicide-related events. For the approved other α2δ ligands, in addition to dizziness, somnolence, and peripheral edema, certain adverse reactions requiring caution have also been reported, including but not limited to: weight gain, ophthalmologic disorders, suicidal behavior and ideation,

angioedema, hypersensitivity, abrupt or rapid discontinuation, abuse potential, congestive heart failure, renal failure, and creatine kinase elevations.

Clinical studies of mirogabalin for CNeP has not been performed yet, however, mirogabalin is expected to have enough efficacy profile in patients with CNeP, in the dose range which are proved to improve PNeP in patient with DPNP and PHN. (see Section 1.2.4).

2. STUDY OBJECTIVES AND HYPOTHESIS

2.1. Study Objectives

2.1.1. Primary Objectives

- To compare change from baseline in the weekly average daily pain score (ADPS) at Week 14 in patients with CNePSCI receiving mirogabalin versus placebo.

2.1.2. Secondary Objectives

- To compare the ADPS responder rate at Week 14 (proportion of subjects with ≥ 30% and ≥ 50% reduction in ADPS from baseline at Week 14) between mirogabalin and placebo
- To evaluate the effect of mirogabalin on additional pain questionnaires, including the Short-Form McGill Pain Questionnaire ([SF-MPQ]: sensory, affective, and total subscales, Visual Analog Scale [VAS], and present pain intensity) and the Neuropathic Pain Symptom Inventory (NPSI)
- To assess the effect of mirogabalin on quality of life (QOL), activities of daily living (ADL), mood, sleep, patient impressions in pain, and allodynia
- To characterize the safety and tolerability of mirogabalin based on weight gain, adverse event (AE), clinical laboratory values, vital sign, 12-lead ECG, medical interview, Columbia-Suicide Severity Rating Scale (C-SSRS), HADS, and edema.

2.1.3. Exploratory Objectives

- To evaluate the effect of mirogabalin on overactive bladder

2.2. Study Hypotheses

The primary hypothesis of this Phase 3 double-blind study is that mirogabalin will be superior to placebo in managing CNePSCI as measured by ADPS and will be generally well tolerated.

2.3. Study Endpoints

2.3.1. Primary Efficacy Endpoint

- Change from baseline in the weekly ADPS at Week 14

2.3.2. Secondary Efficacy Endpoint(s)

- ADPS Responder rate defined as the proportion of subjects with ≥ 30%, and ≥ 50% reduction from baseline to Week 14
- Change from baseline in parameters assessed using SF-MPQ

- Change from baseline in scores assessed using the NPSI
- Change from baseline in average daily sleep interference score (ADSIS)
- Change from baseline in Medical Outcomes Study (MOS) sleep scale including average time to fall asleep, average sleep time per night, and the 5-point scales related to sleep disturbance
- Change from baseline in the Hospital Anxiety and Depression Scale (HADS)
- Changes from baseline in parameters assessed using the Five Level EQ-5D version (EQ-5D-5L)
- Changes from baseline in parameters assessed using the SCI Measure (SCIM III)
- Patient Global Impression of Change (PGIC)
- Change from baseline in allodynia

Details on how to calculate the secondary efficacy endpoints and impute the missing data will be specified in the statistical analysis plan (SAP).

2.3.3. Exploratory Efficacy Endpoint

- Change from baseline in the average daily micturition frequency
- Change from baseline in the average daily urinary incontinence episodes
- Change from baseline in parameters assessed using Overactive Bladder Symptom Score (OAB-SS)

Details on how to calculate the exploratory endpoints and impute the missing data will be specified in SAP, etc.

2.3.4. Pharmacokinetic/Pharmacodynamic/Biomarker Endpoint(s)

Not Applicable.

2.3.5. Safety Endpoint(s)

Treatment-emergent AEs, clinical laboratory tests, vital signs, body weight, 12-lead ECG, edema, C-SSRS, and HADS

2.3.6. Other Endpoints

Not Applicable.

3. STUDY DESIGN

3.1. Overall Design

3.1.1. Study Type

This is a multinational, randomized, double-blind, placebo-controlled, parallel-group Phase 3 study for treatment of CNePSCI.

Study sites: Approximately 120 study sites in Japan, Korea, Taiwan.

Planned sample size: Approximately 274 subjects will be randomized in the study.

3.1.2. Study Scheme

The planned study duration will be approximately 16 weeks, consisting of 1-week observation period, 14-week treatment period, and 1-week follow-up period after last dose. After completion of the observation period, the eligible patients will be randomized into one of 2 arms, placebo or mirogabalin at the ratio of 1:1, respectively. The randomization will be stratified with the factors of baseline ADPS (< 6.0 or ≥ 6.0) and region (Japan and others).

The duration of investigational product administration will be 14 weeks, consisting of a titration period and a maintenance dose period. During the treatment period, 1 tablet of either mirogabalin or matching placebo will be administered orally BID (in the morning and at bedtime).

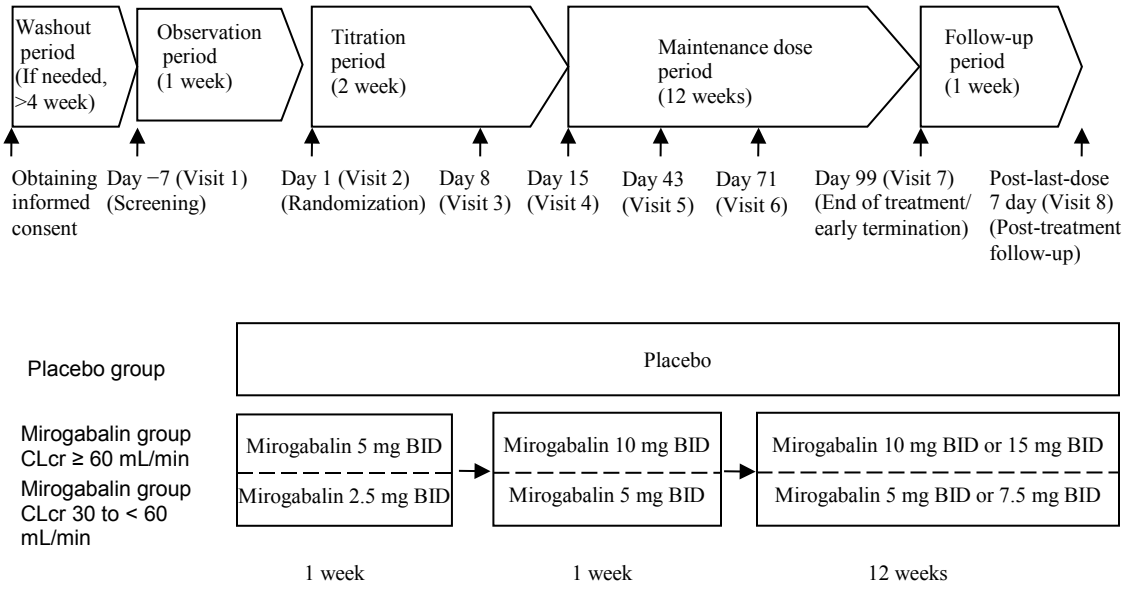
Written informed consent should be obtained before starting any examination and observations to be performed at Visit 1. After informed consent is obtained, patients who are under treatment with mirogabalin, pregabalin, or gabapentin will undergo a washout period of 28 days or more (see Section 5.6.1). Enrollment will be limited to subjects who meet the inclusion/exclusion criteria described in Section 4.1 and Section 4.2.

In mirogabalin group, patients with CLcr ≥ 60 mL/min at screening will start with 5 mg BID of mirogabalin at first week, followed by 10 mg BID at second week as titration phase. From the third week, if there are no problems in safety, the patients will escalate the dose to 15 mg BID. For the following visits, the dosage may be changed to either 10 mg BID or 15 mg BID depending on safety findings at the time of each visit. Patients in placebo group take matching placebo throughout the entire period.

In mirogabalin group, patients with CLcr 30 to < 60 mL/min at screening, will start 2.5 mg BID of mirogabalin at first week, followed by 5 mg BID at second week as titration phase. From the third week, if there are no problems in safety, the patients will escalate the dose to 7.5 mg BID. For the following visits, the dosage may be changed to either 5 mg BID or 7.5 mg BID depending on safety findings at the time of each visit. Patients in placebo group take matching placebo throughout the entire period.

After the completion or early termination of administration, subjects will be monitored for an additional follow-up observation period of 1 week. Follow-up observation is not required for subjects who are enrolled in an open-label extension study.

Further details of the study procedures are provided in the Schedule of Events (See Section 17.1) and Study Procedures (See Section 6).



3.2. Discussion of Study Design

3.2.1. Dosage of Mirogabalin

Mirogabalin was administered at doses of 15 mg QD, 10 mg BID, or 15 mg BID in Asian patients with DPNP and PHN as a separate Phase 3 study. The total study duration for an individual patient was approximately 16 weeks, consisting of an observation period (1 week), a titration period (1 to 2 weeks), a fixed-dose period (12 to 13 weeks), and a follow-up period (1 week). In the study with both DPNP and PHN, the mean ADPS at Week 14 decreased from baseline in all treatment groups. The efficacy of 15-mg BID was superior to placebo in the change in ADPS from baseline at Week 14 in the both study with DPNP and PHN. For the efficacy of 10-mg BID, a certain pain improvement effect was also shown in the both study with DPNP and PHN. Safety analysis of DPNP and PHN studies showed mirogabalin was tolerated at all dose.

To evaluate the effect of CLcr on mirogabalin exposure, population pharmacokinetic (PK) analysis was performed using result of clinical pharmacology studies in subjects with renal impairment (see Section 1.2.3.4). Relative to subjects with normal renal function (≥ 90 mL/min), total clearance of mirogabalin was predicted about 11%, 56%, and 73% lower than in subjects with mild (60 to 89 mL/min), moderate (30 to 59 mL/min), and severe (15 to 29 mL/min) renal impairment, respectively. Based on the results, a half dose in subjects with moderate renal impairment were expected to be equivalent exposure to a dose in subjects with normal renal function.

Based on these results, the dosage and administration of the Japanese package insert for PNeP indication is as follows; “Usually, for adults, administer mirogabalin at an initial oral dose of 5 mg twice daily, and then increase the dose by 5 mg per dosing with an interval of at least 1 week up to 15 mg twice daily. The dose may be increased or

decreased appropriately in the range between 10 mg and 15 mg twice daily, based on individual patient age or symptoms." For patients with CLcr ≥ 60 mL/min, 5 mg BID will be the initial dose, 10 mg BID will be the lowest effective dose, and 15 mg BID will be the recommended effective dose. For patients with CLcr 30 to < 60 mL/min, 2.5 mg BID will be the initial dose, 5 mg BID will be the lowest effective dose, and 7.5 mg BID will be the recommended effective dose.

Nonclinical trial in using rat with spinal cord injury as typical experimental CNePSCI model indicated that mirogabalin single dose significantly improved mechanical allodynia of the rat, and time course and effective dose of analgesic effect in the CNePSCI rat model are similar that of analgesic effect in PNeP rat model. In addition, clinical studies of pregabalin, which has the same mechanism of action of mirogabalin, in patients for PNeP and CNePSCI showed same efficacy and safety profile in both PNeP and CNePSCI, in the same dose range.

Therefore, the dosage of mirogabalin in this study is selected as the same dosage as the possible dose regimen in the Japanese package insert. Dosage of mirogabalin for CNePSCI patients with CLcr ≥ 60 mL/min is 5 mg BID at first week, followed by 10 mg BID at second week as titration phase, and from the third week, if there are no problems in safety, escalated to 15 mg BID. For the following visits, the dosage may be changed to either 10 mg BID or 15 mg BID depending on safety findings. Dosage of mirogabalin for CNePSCI patients with CLcr 30 to < 60 mL/min is 2.5 mg BID at first week, followed by 5 mg BID at second week as titration phase, and from the third week, if there are no problems in safety, escalated to 7.5 mg BID. For the following visits, the dosage may be changed to either 5 mg BID or 7.5 mg BID depending on safety findings.

3.2.2. Duration of Study Treatment

In the double-blind study, the efficacy of mirogabalin versus placebo in CNePSCI, one of the typical NeP will be evaluated. The European Medicines Agency (EMA) guideline[13] recommends that the treatment duration for maintenance dose period be 12 weeks or longer. Therefore, the study will have 12 weeks of maintenance dose period. In addition, taking into consideration for subject safety, the study will have 2 weeks of titration period before the maintenance dose period.

3.2.3. Control Treatment

Placebo will be used as the control treatment in the study. Inclusion of placebo is required in the EMA guideline.[13]

3.2.4. Study Endpoints

In accordance with recommendations from the EMA guideline,[13] the primary endpoint was selected as amount of change in findings on an 11-point pain scale. Patients with CNePSCI can experience seriously decreased QOL, ADL, not only from pain but also from factors such as poor sleep. Moreover, it seems that pain reduction by mirogabalin may improve the QOL and the ADL of the subjects. To assess these factors, secondary endpoints were selected in areas such as sleep, QOL and ADL.

4. STUDY POPULATION

4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria to be included in the study.

1. Age ≥ 20 years at informed consent
2. Able to give informed consent for the study participation, understand procedures of this study, and complete patient-reported questionnaires adequately
3. SCI due to trauma (eg, turnover, fall, traffic accident, sports accident)
4. C4-T12 spinal cord injury identified on MRI
5. American Spinal Injury Association (ASIA) impairment scale A, B, C, or D
6. NeP region expressed at level and/or below level of spinal cord injury
7. ≥ 6 months after SCI at screening
8. Stable CNePSCI at least for 3 months prior to screening
9. At screening, a pain scale of ≥ 40 mm on VAS of SF-MPQ
10. At randomization, a pain scale of ≥ 40 mm on VAS of SF-MPQ, and completion of at least 4 days of daily pain diaries with an ADPS of ≥ 4 over the past 7 days on the 11-point Numerical Rating Scale (NRS)

Rationale

1.: Phase 1, Phase 2 and Phase 3 studies in elderly subjects showed no notable differences from the results obtained in non-elderly subjects with regard to safety, tolerability, and PK. Thus, no upper limit was placed on age in this study. Because the safety of this drug have not been established in children, and in order to obtain appropriate informed consent from the subjects themselves, the lower age limit was set at 20 years of age.

2.: The study will be conducted in accordance with Good Clinical Practice (GCP).

3., 4., 5., 6., 7., 8.: The study will investigate CNePSCI.

9., 10.: In order to assess the efficacy of the investigational product appropriately, the study will be limited to subjects who experience pain of moderate or greater intensity.

4.2. Exclusion Criteria

Subjects who meet any of the following criteria will be disqualified from entering the study:

1. On any one day during the observation period, pain score of 10 on a scale of 0 (no pain) to 10 (worst possible pain)
2. Other severe pain at screening or randomization, unrelated to CNePSCI, that may confound the assessment of CNePSCI

3. Neurologic disorders at screening or randomization, unrelated to CNePSCI, that may confound the assessment of CNePSCI
4. Major psychiatric disorders within 1 year prior to screening
5. Patient who has secondary-gain from CNePSCI (eg, legal dispute or settlement negotiations) at screening or randomization
6. SCI due to suicidal behavior
7. Patient who blames the third party for his/her spinal cord injury, in the case of spinal cord injury due to the third party act (Those patients can rarely overcome the pain due to the psychiatric factor)
8. Previous administration of pregabalin ≥ 300 mg/day for subjects with CLcr (using the Cockcroft-Gault) ≥ 60 mL/min or ≥ pregabalin 150 mg/day for subjects with CLcr 30 to < 60 mL/min for at least 4 weeks, declared lack of effect
9. Previous administration of gabapentin ≥ 1200 mg/day for subjects with CLcr ≥ 60 mL/min or gabapentin ≥ 600 mg/day for subjects with CLcr 30 to < 60, for at least 4 weeks, declared lack of effect
10. Use of mirogabalin, pregabalin, or gabapentin within 28 days prior to screening
11. Use of strong opioids for analgesic of CNePSCI within 3 months prior to screening
12. CLcr (using the Cockcroft-Gault equation) < 30 mL/min at screening
13. Malignancy other than basal cell carcinoma within the past 2 years prior to screening
14. Clinically significant unstable endocrine (eg, diabetes mellitus), neurologic, ophthalmologic, hepatobiliary, respiratory, hematologic illness, or cardiovascular disease (eg, uncontrolled cardiac arrhythmia, or myocardial infarction) at screening or randomization
15. Clinically significant findings on electrocardiogram (ECG) at screening
16. History of pernicious anemia, untreated hypothyroidism, or human immunodeficiency virus infection
17. Pregnancy, potential pregnancy, breast feeding, or subject unwilling to take reliable contraceptive measures during the study or for 4 weeks after study completion
18. Known hypersensitivity to mirogabalin, pregabalin, or gabapentin
19. Participation in another clinical study, either currently or within 30 days prior to providing of informed consent
20. Experience of participating mirogabalin clinical study and receiving investigational product
21. Abuse of illicit drugs or alcohol history

22. Response of "yes" to any of the questions on the C-SSRS at screening or randomization in relation to events occurring within the past 12 months
23. At screening, clinical laboratory values exceeding limits listed in Table 4.1
24. The subject who is considered inappropriate for the study at the discretion of the investigator or sub-investigator

Rationale

1.: This criteria was selected so that efficacy could not be appropriately assessed in these subjects, because reporting extreme pain may reflect psychosocial distress, and may reflect patients' lack of comprehension to accurately rate their pain.

2., 3., 4., 5., 6., 7., 10.: These criteria were selected so that efficacy and safety could be appropriately assessed in subjects.

8., 9., 11: These criteria were selected out of consideration for efficacy assessment in subjects.

12., 13., 14., 15., 16., 17., 18., 19., 20., 21., 22., 23., 24.: These criteria were selected out of consideration for the safety of subjects.

Table 4.1: Hematology/Blood Chemistry Limits

Hematology	Platelet Count	< 100,000/mm^3
Blood Chemistry	AST (GOT)	> 2.0 × ULN
	ALT (GPT)	> 2.0 × ULN
	ALP	> 1.5 × ULN
	T-Bil	> 1.5[a] × ULN

a: If a subject has T-Bil 1.5 > ULN: unconjugated and conjugated bilirubin fractions should be analyzed and only subjects documented to have Gilbert's syndrome may be enrolled.

5. STUDY TREATMENT(S)

5.1. Assigning Subjects to Treatments and Blinding

5.1.1. Treatment Group(s)/Sequences

After completion of the observation period, the eligible patients will be randomized into one of 2 arms, placebo or mirogabalin at the ratio of 1:1, respectively. The duration of investigational product administration will be 14 weeks, consisting of a titration period and a maintenance dose period.

In mirogabalin group, patients with CLcr ≥ 60 mL/min at screening, will start with 5 mg BID of mirogabalin at first week, followed by 10 mg BID at second week as titration phase. From the third week, if there are no problems in safety, the patients will escalate the dose to 15 mg BID. For the following visits, the dosage may be changed to either 10 mg BID or 15 mg BID depending on safety findings at the time of each visit. Patients in placebo group take matching placebo throughout the entire period.

In mirogabalin group, patients with CLcr 30 to < 60 mL/min at screening, will start 2.5 mg BID of mirogabalin at first week, followed by 5 mg BID at second week as titration phase. From the third week, if there are no problems in safety, the patients will escalate the dose to 7.5 mg BID. For the following visits, the dosage may be changed to either 5 mg BID or 7.5 mg BID depending on safety findings at the time of each visit. Patients in placebo group take matching placebo throughout the entire period.

5.1.2. Method of Treatment Allocation

5.1.2.1. Enrollment

Subjects are to be enrolled in this study using the Interactive Response Technology (IRT) in accordance with the procedures specified below. IRT will assign each consenting subject a unique subject identification code, and that identification code will be recorded in a subject identification log.

5.1.2.2. Procedures for Subject Enrollment

The investigator or sub-investigator will perform a mandatory interview to assess the eligibility of subjects for the study, after obtaining each subject's written informed consent, and will make necessary entries in the IRT at screening. When conducting overactive bladder evaluation (exploratory evaluation for only Japanese subjects with self-urination), informed consent for the evaluation also must be obtained. Any subjects who have been taking prohibited concomitant drugs will undergo a washout period (see Section 5.6.1), prior to the observation period. After the screening visit (Visit 1), a 7-day observation period will be implemented before randomization.

At randomization (Visit 2), after completion of the observation period, the investigator or sub-investigator will again perform a mandatory interview to assess the eligibility of subjects for the study and will make necessary entries in the subject registration system.

The subject who are considered to be eligible for participation in the study, on the basis of evaluation prior to randomization, will be randomized to one of the mirogabalin-arm or placebo-arm at the ratio of 1:1, with stratification factors of baseline ADPS (< 6.0 or ≥ 6.0) and region (Japan or the others). The randomization schedule for the IRT will be generated by the independent biostatistician. The investigational product for each study drug identifier will be dispensed specifically to 1 subject, and will not be used by any other subjects.

If the enrolled subject is confirmed to be eligible, the investigator or sub-investigator will be notified of the study drug identifier assigned to the subject by the IRT. The investigator or sub-investigator will confirm the reported study drug identifier, and will assign the investigational products labeled with the study drug identifier for the subject.

If the subject is considered ineligible for the study, the investigator or sub-investigator will inform the subject, and will provide standard care.

5.1.3. Blinding

The study will be a double-blind study, using matching placebo. Blinding will be applied to all personnel related to the study (subjects, investigators, sub-investigators, sponsor, and contact research organization), with the exception of the independent biostatistician, the independent sub-functional lead of biostatistics (ISFLB), and other staff involved in the preparation, release and shipment of IMP.

Randomization schedule will be generated by the independent biostatistician and approved by the ISFLB. The independent biostatistician will share the randomization schedule with personnel specified in the randomization schedule request form. Until the study is unblinded, the randomization schedule will be kept securely.

5.1.4. Emergency Unblinding Procedure

In the case of an emergency where, in the opinion of the Investigator, discontinuation of study drug is not sufficient and the study treatment must be unblinded in order to evaluate further a course of medical treatment, the Investigator can perform the unblinding by directly accessing the IRT.

In the event of an emergency unblinding, the subject will be informed about their treatment assigned. Information about the treatment assignment must be restricted to designated study site staff/ personnel who are providing immediate care to the subject. Any documentation of the treatment assignment must be maintained separately (ie, a secured file). The information must not be included in the subject's source files to ensure the treatment assignment will remain blinded to the study monitors and other study personnel not involved with the subject's immediate care.

Once the study treatment has been unblinded for a specific subject, the study treatment should be discontinued for the subject, and the subject should leave the study treatment phase. The end of treatment and follow-up assessments for the subjects will be performed as defined in the protocol.

5.2. Study Drug(s)

5.2.1. Description

The investigator must ensure that the investigational product will be used only in accordance with the protocol.

The investigational products for this study are:

- Mirogabalin 2.5 mg, 5 mg, 7.5 mg, 10 mg, and 15 mg tablets
- Placebo tablets matching mirogabalin 2.5 mg, 5 mg, 7.5 mg, 10 mg, and 15 mg tablets

For details and handling of the investigational product, refer to the Investigator's Brochure, and the manual for management of the investigational product.

5.2.2. Labeling and Packaging

Mirogabalin and matching placebo, will be packaged in aluminum blister packs. Packages for treatment period will be prepared for the combinations shown in Table 5.1, Table 5.2, and Table 5.3. The packaging will be clearly labeled "For Clinical Study Use Only," and will show the display name of the investigational product, the investigational-product-manufacturing code, the study drug identifier, the name and address of the sponsor, and the expired date of the investigational product in accordance with local regulations. Each wallet card of the investigational product will contain sufficient extra doses to cover the permitted visit window for each subject.

Table 5.1: Drug Combinations During the Treatment Period (Week 1)

Treatment group	Investigational product combination	
	Morning	Bedtime
Mirogabalin group CLcr ≥ 60 mL/min	5	5
Mirogabalin group CLcr 30 to < 60 mL/min	2.5	2.5
Placebo	P	P

5: mirogabalin 5 mg tablet
2.5: mirogabalin 2.5 mg tablet
P: mirogabalin matching placebo tablet

Table 5.2: Drug Combinations During the Treatment Period (Week 2)

Treatment group	Investigational product combination	
	Morning	Bedtime
Mirogabalin group CLcr ≥ 60 mL/min	10	10
Mirogabalin group CLcr 30 to < 60 mL/min	5	5
Placebo	P	P

10: mirogabalin 10 mg tablet
5: mirogabalin 5 mg tablet
P: mirogabalin matching placebo tablet

Table 5.3: Drug Combinations During the Treatment Period (Week 3 to Week 14)

Treatment group	Investigational product combination	
	Morning	Bedtime
Mirogabalin group CLcr ≥ 60 mL/min	10 or 15	10 or 15
Mirogabalin group CLcr 30 to < 60 mL/min	5 or 7.5	5 or 7.5
Placebo	P	P

10: mirogabalin 10 mg tablet, 15: mirogabalin 15 mg tablet
5: mirogabalin 5 mg tablet, 7.5: mirogabalin 7.5 mg tablet
P: mirogabalin matching placebo tablet

5.2.3. Preparation

Preparation of the study drug is detailed in the Pharmacy Manual.

5.2.4. Administration

During the treatment period, 1 tablet of either mirogabalin or matching placebo will be administered orally BID (in the morning and at bedtime), as shown in Table 5.4.

Table 5.4: Method of Administration During the Treatment Period

Group	Day 1		Day 2 to 7		Day 8		Day 9 to 14		Day 15		Day 16 to 98		Day 99	
	Morning	Bedtime	Morning	Bedtime	Morning	Bedtime	Morning	Bedtime	Morning	Bedtime	Morning	Bedtime	Morning	Bedtime
Mirogabalin CLcr ≥ 60 mL/min	-	5	5	5	5	10	10	10	10	10 or 15	10 or 15	10 or 15	10 or 15	-
Mirogabalin CLcr 30 to < 60 mL/min	-	2.5	2.5	2.5	2.5	5	5	5	5	5 or 7.5	5 or 7.5	5 or 7.5	5 or 7.5	-
Placebo	-	0	0	0	0	0	0	0	0	0	0	0	0	-

5.2.5. Storage

Up to 25°C; do not freeze (excursion permitted up to 30°C).

Drug supplies must be stored appropriately in a locked cabinet in a room with limited and controlled access under the recommended storage conditions.

If storage conditions go outside of the recommended storage conditions, the site must not dispense the affected supplies (affected supplies should be placed in quarantine) and must contact Daiichi Sankyo Clinical Supply Operations personnel or designee to determine if the affected supplies can be used.

5.2.6. Drug Accountability

When a drug shipment is received, the Investigator or designee will check the amount and condition of the drug, check for appropriate local language in the label, drug expiration date, and sign the Receipt of Shipment Form provided.

In addition, the Investigator or designee shall contact Sponsor as soon as possible if there is a problem with the shipment.

A Drug Accountability Record will be provided for the study drug. The record must be kept current and should contain the dates and quantities of study drug received, subject's (identification number or supply number as applicable), for whom the study drug was dispensed, the date and quantity of study drug dispensed and remaining, as well as the initials of the dispenser.

At the end of the study, or as directed, all study drug with all discrepancy resolved, including unused, partially used, or empty containers, will be returned to a designee as instructed by Sponsor. Study drug will be returned only after the study monitor has completed a final inventory to verify the quantity to be returned. The return of study drug must be documented and the documentation included in the shipment. At the end of the study, a final study drug reconciliation statement must be completed by the Investigator or designee and provided to the Sponsor.

5.3. Control Treatment

Placebo will serve as control treatments. Inclusion of placebo is required in light of the known placebo effect in pain studies.

5.4. Dose Interruptions and Reductions

Dose interruption will be occurred only if investigators or sub-investigators decide administration should be interrupted due to safety concerns. During a maintenance dose period, dose will be reduced from 15 mg BID to 10 mg BID or from 7.5 mg BID to 5 mg BID in patients with CLcr $\geq$ 60 mL/min or CLcr 30 to < 60 mL/min respectively, only if drug related adverse events occur and investigators or sub-investigators judge continuation of 15 mg BID or 7.5 mg BID dosing is difficult due to the adverse events.

5.5. Method of Assessing Treatment Compliance

All subjects in this study will commence therapy as outpatients or inpatients, and the investigational product will be self-administered orally. Subjects will be sent home with the investigational product. Each subject is to return the investigational product at every visit. Compliance will be assessed by returned tablet count. Administration of the investigational product will be recorded in the electronic case report form (eCRF)/Drug Accountability Record (number of tablets taken) at all treatment visits. If no tablets are returned, the subject will be asked whether any were discarded or thrown away, or if all of the tablets were taken orally.

5.6. Concomitant Medications

Any concomitant medications and any concomitant treatments conducted to a subject (except for subjects who are withdrawn prior to randomization but after signing informed consent) during the period from the time of obtaining informed consent until Visit 8, will be documented in the case report form (CRF). The route of administration, the total daily dose, the duration of use, the indication for use, and the classification of therapies will also be documented in the CRF.

5.6.1. Prohibited Concomitant Medications

The following drugs are prohibited for concomitant use from the screening (Visit 1) through the post-treatment follow-up (Visit 8). After informed consent is obtained, subjects who are under treatment with Mirogabalin, Pregabalin, or Gabapentin will undergo for 28 days as a minimum washout period. Visit 1 will occur after completion of this washout period.

- Mirogabalin, Pregabalin, and Gabapentin
- Strong opioids
- Other investigational products

5.6.2. Restricted Concomitant Medications

The following drugs are permitted for concomitant use if their dosage has not changed for 28 days prior to Visit 1. These drugs may be used concomitantly from the screening (Visit 1) through Visit 7, but the dosage may not be changed.

- Antiepileptics except for gabapentin and pregabalin
- Antidepressants
- Hypnotics, anxiolytics
- Tramadol
- Neurotropin®
- N-methyl-D-aspartate receptor antagonists (dextromethorphan, ketamine, memantine, etc.)

- Non-steroidal anti-inflammatory drugs (Acceptable for external use and for purposes other than CNePSCI analgesia)
- Muscle relaxants
- Topical capsaicin for analgesic of CNePSCI
- Local anesthetics for analgesic of CNePSCI (lidocaine, etc.)
- Na channel blockers (mexiletine, etc.)
- Centrally acting sympatholytic agents (clonidine, etc.)
- Steroids for analgesic of CNePSCI
- Cilostazol, prostaglandin (Acceptable for external use and for purposes other than CNePSCI analgesia)
- Baclofen

5.6.3. Rescue Medications

Acetaminophen will be permitted as a "rescue medication," to be used when in need of treatment for CNePSCI, and not to exceed the maximum dose stipulated in the package insert. Each subject should record dose(s) of acetaminophen used in the patient diary from Visit 1 to Visit 7, if he/she takes acetaminophen.

5.6.4. Restricted Concomitant Therapies

The following therapies are permitted for concomitant use if their frequency has not changed for 28 days prior to Visit 1. These therapies may be used concomitantly from the screening (Visit 1) through Visit 7, but the frequency may not be changed.

1. Nerve blocks
2. Laser therapy
3. Acupuncture treatment
4. Spinal cord stimulation
5. Surgery that might confound the assessment of CNePSCI
6. Psychological approach (eg, psychoeducation, behavioral therapy, cognitive-behavioral therapy)
7. Rehabilitation (eg, physical therapy, occupational therapy)
8. Other forms of pain reduction therapy that might confound the assessment of CNePSCI

5.6.5. Other

Subjects should be instructed to avoid excessive consumption of alcohol during the treatment period, as combination with investigational drugs and alcohol may enhance impaired attention and impaired equilibrium function.

5.7. Subject Withdrawal/Discontinuation

5.7.1. Withdrawal Criteria

If a subject meets the following withdrawal criteria, that subject should discontinue the study treatment and the study.

- Difficulty of continuing the study due to AE
- AE related to suicide (if there are any "yes" responses to any of the questions in the C-SSRS)
- Subjects with any of the following elevations in clinical laboratory values
  - Increase in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 5 × upper limit of normal (ULN)
  - ALT or AST rises to ≥ 3 × ULN and persists for more than 2 weeks
  - Concurrent increases in ALT or AST ≥ 3 × ULN and total bilirubin (T-Bil) ≥ 2 × ULN
  - ALT or AST ≥ 3 × ULN associated with a clinical presentation suggestive of liver injury (ie, including the appearance of fatigue, nausea, vomiting, jaundice, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia)
- Withdrawal by subject (ie, withdrawal of consent)
- Major protocol deviation (difficulty of continuing the study in terms of ensuring safety of subjects)

5.7.2. Reasons for Withdrawal

If a subject is withdrawn from the study, the date and the reason for withdrawal must be recorded on the eCRF using the following options. If the subject receiving at least one study medication and withdrew/was withdrawn from the study treatment, the reason for the withdrawal of study treatment must be recorded on the eCRF.

For subjects withdrawn prior to enrollment but after signing informed consent

- Screen Failure
- Withdrawal by Subject (eg, AE, lack of efficacy [LOE], Other)
- Physician Decision
- Other

For subjects withdrawn after randomization but before completing the study as per protocol

- AE
- Death

- LOE
- Lost to Follow-up
- Protocol violation
- Pregnancy
- Study Terminated by Sponsor
- Withdrawal by Subject (eg, AE, LOE, Other)
- Other

If a subject is withdrawn due to need for a prohibited medication, the reason may be recorded as LOE, as appropriate. Reasons recorded under "Protocol violation" may include failure to comply with protocol requirements or study procedures.

For all subjects who withdraw from the study, the investigator must complete and report pertinent observations as thoroughly as possible up to the date of withdrawal, including the date of last treatment and the reason for withdrawal.

If a subject is withdrawn due to an AE, the investigator should follow the subject until the AE has resolved or stabilized.

All subjects who are withdrawn from the study should complete protocol-specified withdrawal procedures (see Section 5.7.3 and Section 6.4).

5.7.3. Withdrawal Procedures

If the subject withdraws or is withdrawn from the study before the completion of investigational product administration, appropriate measures will be implemented. In addition, to the extent that the subject's cooperation can be obtained, all observations and tests scheduled for the End of Treatment (Visit 7)/Early Termination Visit will be conducted, assessments will be made at that time point, all observations and tests scheduled for the Post-treatment Follow-up Visit (Visit 8) will be conducted, and assessments will be made 5 to 14 days after the last dose. This will be done for all subjects who were treated with even one dose of the investigational product. If the withdrawal was due to AEs, the outcome for that subject will be recorded to the extent possible in the CRF. If the withdrawal was due to suicidal behavior and/or suicidal ideation, appropriate measures will be implemented such as referring the subject to a specialist.

5.7.4. Subject Replacement

Subjects removed from the study for any reason will not be replaced.

5.7.5. Subject Re-screening Procedures

Re-screening is allowed to only subjects who violate Inclusion Criteria 4, Exclusion Criteria 10, 12, 19, or 23, only if the subjects are not randomized. The re-screening is permitted only once.

6. STUDY PROCEDURES

A study visit schedule in tabular format is provided in Section 17.1.

In principle, all of the activities and/or examinations will be recorded with the date in the CRF.

Missing visits are strongly discouraged in this study. It is expected that investigator site staff thoroughly explain the visit schedule with potential subjects. If it is felt that a subject is not able to adhere to the visit schedule, then that subject should not be randomized into the study. Any missed visit that occurs during the double-blind treatment period must be rescheduled within 1 week.

6.1. Screening (Visit 1)

Written informed consent should be obtained before starting any examination and observations to be performed at Visit 1. After informed consent is obtained, patients who are under treatment with mirogabalin, pregabalin, or gabapentin will undergo a washout period of 28 days or more (Section 5.6.1). The following activities and/or examinations will be performed at screening.

- Evaluate inclusion criteria and exclusion criteria
- Record demographics (birth date, sex, causality of SCI [turnover, fall, traffic accident, sports accident, or other], type of SCI [quadriplegia or paraplegia], site of SCI [C4-C8, T1-T12], duration of SCI, duration of CNePSCI, NeP region [at level or below level], medical/surgical history related to exclusion criteria)
- Identify SCI by MRI
  - If SCI has been identified previously on MRI, MRI inspection for this study is not needed.
- Conduct ASIA International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) and evaluate ASIA impairment scale
- Provide explanation regarding patient diaries including pain and sleep interference, and issue the diaries
- Complete SF-MPQ
- Complete HADS
- Measure body height and weight
- Perform medical interview
- Perform evaluation of edema
- Measure blood pressure and pulse rate
- Perform 12-lead ECG
- Collect blood and urine samples for laboratory tests

- Evaluate serious AEs (SAEs)
- Complete C-SSRS
- Perform pregnancy test (only in women of childbearing potential)
- Evaluate prior drug treatment, concomitant drugs, and concomitant therapy
- Complete OAB-SS (for only Japanese subjects with self-urination)
- Provide explanation regarding bladder diary, and issue the diary (for only Japanese subjects with self-urination, and who meet the diagnostic criteria of overactive bladder in OAB-SS)

6.2. Randomization (Visit 2)

Subjects will be randomized to treatment groups after screening. The following activities and/or examinations will be performed at randomization.

- Evaluate inclusion criteria and exclusion criteria
- Collect and review patient diaries
- Measure body weight
- Perform medical interview
- Measure blood pressure and pulse rate
- Collect blood and urine samples for laboratory tests
- Evaluate SAEs
- Complete C-SSRS
- Complete HADS
- Record and evaluate concomitant drugs and concomitant therapy
- Confirm eligibility and randomization
- Issue the investigational product
- Issue the patient diaries
- Complete SF-MPQ
- Complete NPSI
- Complete MOS sleep scale
- Complete EQ-5D-5L
- Complete SCIM
- Perform evaluation of allodynia

- Collect and review bladder diary (for only Japanese subjects with self-urination, and who meet the diagnostic criteria of overactive bladder in OAB-SS at Visit 1)

6.3. Treatment Period

The treatment period will be 14 weeks in duration.

6.3.1. Visit 3 and Visit 4

From Visit 2 to Visit 4, subjects will come to the study site every week (Visit 3, Visit 4). The investigator or sub-investigator will confirm tolerability and review continuation of the treatment before issuing the new investigational product. The following activities and/or examinations will be performed at Visit 3 and Visit 4.

- Collect and review patient diaries
- Measure body weight
- Perform medical interview
- Measure blood pressure and pulse rate
- Collect blood and urine samples for laboratory tests
- Complete SF-MPQ
- Complete C-SSRS
- Complete HADS
- Evaluate AEs
- Record and evaluate concomitant drugs and concomitant therapy
- Collect unused investigational product and record and review drug-taking compliance
- Record the date of the first dose taken (only Visit 3)
- Issue the investigational product
- Issue the patient diaries

6.3.2. Visit 5 and Visit 6

From Visit 4 to Visit 6, subjects will come to the study site once every 4 weeks (Visit 5, Visit 6). The investigator or sub-investigator will confirm tolerability and review continuation of the treatment before issuing the new investigational product. The following activities and/or examinations will be performed at Visit 5, and Visit 6.

- Collect and review patient diaries
- Measure body weight
- Perform medical interview

- Measure blood pressure and pulse rate
- Collect blood and urine samples for laboratory tests
- Complete SF-MPQ
- Complete C-SSRS
- Complete HADS
- Evaluate AEs
- Record and evaluate concomitant drugs and concomitant therapy
- Collect unused investigational product and record and review drug-taking compliance
- Issue the investigational product
- Issue the patient diaries
- Issue bladder diary (for only Japanese subjects with self-urination, and who meet the diagnostic criteria of overactive bladder in OAB-SS at Visit 1); only Visit 6

6.4. End of Treatment (Visit 7)/Early Termination

The treatment period will be completed at Visit 7. The following activities and/or examinations will be performed at the end of treatment/early termination.

- Collect and review patient diaries
- Conduct ASIA ISNCSCI and evaluate ASIA impairment scale
- Measure body weight
- Perform medical interview
- Evaluation of edema
- Perform evaluation of allodynia
- Measure blood pressure and pulse rate
- Perform 12-lead ECG
- Collect blood and urine samples for laboratory tests
- Complete C-SSRS
- Complete HADS
- Perform pregnancy test (only in women of childbearing potential)
- Evaluate AEs
- Record and evaluate concomitant drugs and concomitant therapy

- Collect unused investigational product and record and review drug-taking compliance
- Record the date of the last dose taken
- Complete SF-MPQ
- Complete NPSI
- Complete MOS sleep scale
- Complete PGIC
- Complete EQ-5D-5L
- Complete SCIM
- Collect and review bladder diary (for only Japanese subjects with self-urination, and who meet the diagnostic criteria of overactive bladder in OAB-SS at Visit 1)
- Complete OAB-SS (for only Japanese subjects with self-urination, and who meet the diagnostic criteria of overactive bladder in OAB-SS at Visit 1)

6.5. Follow-up

Follow-up observations will be conducted 7 days after the completion of administration (Visit 8). The following activities and/or examinations will be performed at post-treatment follow-up. No follow-up observation is required for subjects enrolled in an open-label extension study.

- Measure body weight
- Perform medical interview
- Measure blood pressure and pulse rate
- Collect blood and urine samples for laboratory tests
- Complete C-SSRS
- Complete HADS
- Evaluate AEs
- Record and evaluate concomitant drugs and concomitant therapy

7. EFFICACY ASSESSMENTS

7.1. Assessments for Efficacy Endpoint(s)

7.1.1. Primary Efficacy Endpoint

7.1.1.1. Change from Baseline in the Weekly Average Daily Pain Score at Week 14[14]

Subjects will record a pain score in the patient diary once daily from the day after Visit 1 through Visit 7. Every morning upon awakening, prior to taking study medication, the subject will check the number that best describes his or her pain over the past 24 hours on a scale of 0 (no pain) to 10 (worst possible pain). The weekly ADPS is defined as being weekly average of the pain scores.

Details on how to calculate the primary efficacy endpoints and impute the missing data will be specified in the SAP.

7.1.2. Secondary Efficacy Endpoint

7.1.2.1. Average Daily Pain Score Response Rate[13]

ADPS Response rate is defined as the proportion of subjects with ≥ 30%, and ≥ 50% reduction from baseline to week 14 in ADPS.

7.1.2.2. Change from Baseline in Parameters Assessed Using Short-Form McGill Pain Questionnaire[15]

At Visit 1, Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, Visit 8, subjects will provide a self-assessment using the SF-MPQ. The SF-MPQ consists of 3 parts:

- Fifteen pain descriptors that are given a score of 0 (none) to 3 (severe) based on intensity. The scores are summarized as a sensory score of 11 descriptors, an affective score of 4 descriptors, and a total score of 15 descriptors.
- A VAS, in which the subject rates pain intensity on a 100 mm-long horizontal line, where 0 mm = no pain and 100 mm = worst possible pain.
- A Present Pain Intensity index that provides a score of 0 to 5 based on intensity

7.1.2.3. Patient Global Impression of Change[14]

At Visit 7, subjects will provide a self-assessment in comparison to Visit 2, using the 7-point scale in the PGIC.

1: very much improved

2: much improved

3: minimally improved

4: no change

5: minimally worse

6: much worse

7: very much worse

Two types of PGIC responder rate are defined as the proportion of subjects who satisfy the following PGIC score:

Minimally improved or better (ie, Score ≤ 3)

Much improved or better (ie, Score ≤ 2)

7.1.2.4. Change from Baseline in Sleep-interference Score

The Daily Sleep Interference Diary consists of an 11-point NRS which will be used to assess how pain has interfered with the subject's sleep during the past 24 hours. Subjects will record a sleep-interference score in the patient diary once daily from the day after Visit 1 through Visit 7. Every morning upon awakening, prior to taking study medication, the subject will select the number that best describes his or her sleep interference experience during the past 24 hours on a scale of 0 (pain did not interfere with sleep) to 10 (pain completely interfered with sleep). The weekly ADSIS is based on the sleep interference scores from the patient daily pain diaries.

7.1.2.5. Change from Baseline in Medical Outcomes Study Sleep Scale[16,17]

At Visit 2 and Visit 7, subjects will provide a self-assessment using the MOS sleep scale. The MOS sleep scale is based on questions about sleep quality during the past 4 weeks, and consists of 3 parts:

- The average time required to fall asleep
  - 0 to 15 minutes.....1
  - 16 to 30 minutes.....2
  - 31 to 45 minutes.....3
  - 46 to 60 minutes.....4
  - More than 60 minutes.....5
- The average hours of sleep per night, given as number of hours per night.

Ten questions that are given a score of 1 (all of the time) to 5 (none of the time), based on sleep disturbance in the following areas: difficulty in falling asleep or remaining asleep, difficulty in staying awake during the day, difficulty in breathing, and snoring during sleep.

Based on the 12 questions above, the following scales will be calculated for the analyses:

- Sleep disturbance
- Snoring
- Awakening due to shortness of breath or due to headache
- Sleep adequacy

- Sleep somnolence
- 9-item sleep problems index
- Sleep quantity
- Optimal sleep

7.1.2.6. Change from Baseline in Hospital Anxiety and Depression Scale[18]

At Visit 2 and Visit 7, subjects will provide a self-assessment using the HADS, which will be adopted as efficacy evaluation. The HADS consists of 7 items to score depression (4-point scale) and 7 items to score anxiety (4-point scale). Two types of subscale, depression and anxiety, will be calculated by the summing the corresponding scores for 7 items.

7.1.2.7. Change from Baseline in Neuropathic Pain Symptom Inventory[19]

At Visit 2 and Visit 7, subject will provide a self-assessment using the NPSI, which reflects four distinct dimensions of NeP: spontaneous pain, paroxysmal pain, evoked pain, and paresthesia/dysesthesia. Each questionnaire in the dimensions has 11-point scale from 0 (no pain) to 10 (the most intense pain imaginable) to report the mean intensity of each of these items during the last 24 hours.

- spontaneous pain: burning, squeezing, and pressure
- paroxysmal pain: electric shock, stabbing
- evoked pain: brushing, pressure, contact with something cold
- paresthesia/dysesthesia: pins and needles, tingling

Additionally, the duration of spontaneous pain (ie number of hours during the last 24 hours) and frequency of paroxysmal pain (ie number of paroxysms during the last 24 hours) will be evaluated.

7.1.2.8. Change from Baseline in Five Level EQ-5D version[20]

At Visit 2 and Visit 7, subjects will provide a self-assessment using the EQ-5D-5L. The questionnaire yields a 5-scale profile of the subject's self-assessed QOL in the following dimension: mobility (5-point scale), self-care (5-point scale), usual activities (5-point scale), pain/discomfort (5-point scale), and anxiety/depression (5-point scale) that are combined into an overall health utilities index, and an Visual Analogue Scale (VAS) that measures perception of overall health, with zero indicating worst health and 100 representing best imaginable health.

7.1.2.9. Change from Baseline in Spinal Cord Independence Measure[21]

At Visit 2 and Visit 7, the investigator, sub-investigator, or site stuff will assess the subjects' ADL using SCIM. The SCIM instrument yield a profile of the subject's ADL in the following categories: total SCIM score (0 to 100), self-care (scored 0 to 20), respiration and sphincter management (0 to 40) and mobility (0 to 40).

7.1.2.10. Change from Baseline in Allodynia

At Visit 2 and Visit 7, the investigator or sub-investigator will perform the test for allodynia ([at level] and [below level]), using the following 2-points scale. The assessments of allodynia are detailed in the Procedures Manual.

1: present

2: absent

7.1.3. Exploratory Efficacy Endpoint

7.1.3.1. Change from baseline in the average daily micturition frequency

Japanese subjects with self-urination, and who meet the diagnostic criteria of overactive bladder in OAB-SS at Visit 1 will record the micturition frequency in the bladder diary from Visit 1 to Visit 2, and from Visit 6 to Visit 7.

7.1.3.2. Change from baseline in the average daily urinary incontinence episodes

Japanese subjects with self-urination, and who meet the diagnostic criteria of overactive bladder in OAB-SS at Visit 1 will record the incontinence episodes in the bladder diary from Visit 1 to Visit 2, and from Visit 6 to Visit 7.

7.1.3.3. Change from baseline in parameters assessed using Overactive Bladder Symptom Score (OAB-SS)[22]

At Visit 1 and Visit 7, subjects will provide a self-assessment using the OAB-SS. The questionnaire yields the micturition frequency from waking in the morning until sleeping at night, the micturition frequency of waking up to urinate from sleeping at night until waking in the morning, frequency of sudden desire to urinate, and frequency of leaking urine.

7.2. Appropriateness of Selected Efficacy Assessment(s)

The primary efficacy endpoint was selected based on the EMA guideline for clinical trial on NeP indication, which recommends the use of an instrument that assesse the average pain over a short period, and no longer than 24 hours. The pain score instrument is validated and is utilized in this manner.

The secondary efficacy endpoints were selected for this study because these endpoints were suitable for assessing the main symptom of CNePSCI (pain) and associated symptoms of CNePSCI (poor sleep, anxiety, depression, etc). Moreover, patients with CNePSCI can experience seriously decreased QOL and ADL from pain or poor sleep. All questionnaires are validated and widely used for clinical trials.

8. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

8.1. Pharmacokinetic Assessment(s)

No PK analysis will be performed.

8.2. Pharmacodynamic Assessment(s)

No pharmacodynamic analysis will be performed.

8.3. Biomarker Assessment(s)

No biomarker analysis will be performed.

8.4. Immunogenicity

No immunogenicity analysis will be performed.

8.5. Pharmacogenomic Analysis

No pharmacogenomic analysis will be performed.

9. SAFETY EVALUATION AND REPORTING

9.1. Assessment of Safety Endpoint(s)

Safety endpoints will be body weight, TEAEs, clinical laboratory tests, vital signs, 12-lead ECG, medical interview, C-SSRS, HADS, and edema.

9.2. Adverse Event Collection and Reporting

All SAEs (see Section 9.4.1 and Section 9.4.2 for definitions) occurring after the subject signs the ICF and up to 7 days after the last dose of study medication (ie, the follow-up period), whether observed by the Investigator or reported by the subject, will be recorded on the AE section in CRF. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

All non-SAEs occurring after the subject has taken the first dose of study medication until 7 days after the last dose of study medication (Visit 8) will be recorded on the AE section in CRF.

When an AE occurs, the investigator or sub-investigator will provide appropriate treatment and to the extent possible will monitor progress until the AE is resolved or resolving. However, the investigator or sub-investigator can terminate the monitoring as the clinical trial after explaining it to the subject that he/she deems medically impossible to resolve it at the end of the study (although the treatment for the AE will be continued). In addition, the investigator or sub-investigator can also terminate it, if he/she decides further follow-up is unnecessary because of an AE for which a causal relationship with the investigational product can be ruled out, or if the subject refuses further follow-up.

Any symptom that the investigator or sub-investigator considers associated with CNePSCI will be evaluated as an efficacy variable and will not be regarded as an AE. However, if the symptom is considered potentially related to the investigational product, such symptom will be regarded as an AE. Medical conditions (including clinically significant laboratory values that are not symptoms of CNePSCI /vital signs that are out of range) that were diagnosed or known to exist prior to the first dose will be recorded as part of medical history.

All AEs, SAEs, and AEs of special interest (AESI) are to be reported according to the procedures in Section 9.5.

Exacerbation of a pre-existing medical occurrence and symptom after the first dose of study medication including increase in severity of the symptom will be recorded as an AE on the AE section, unless it is the condition of CNePSCI.

All clinical laboratory results, vital signs, and ECG results or findings should be appraised by the Investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or ECG findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, dose reduction, require corrective treatment, or constitute an AE in the Investigator's clinical judgment.

At each visit, the Investigator will determine whether any AEs have occurred by evaluating the subject. AEs may be directly observed, reported spontaneously by the subject or by questioning the subject at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 9.4. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the ICF) procedures or treatments requiring hospitalization for pre-existing conditions that do not worsen in severity should not be reported as SAEs (see Section 9.4.2 for Definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any serious, untoward event that may occur subsequent to the reporting period that the Investigator assesses as related to study drug should also be reported and managed as an SAE.

9.3. Adverse Events of Special Interest

All antiepileptic drugs carry a risk of increased suicidal behavior and ideation. Furthermore, increased hepatic transaminases have been observed in the mirogabalin development program. Therefore, the following "suicidal behavior and ideation" and "liver enzyme elevations/liver dysfunction" will be treated as AESI.

- Increase in ALT or AST $\geq 5 \times$ ULN
- ALT or AST rises to $\geq 3 \times$ ULN and persists for more than 2 weeks
- Concurrent increases in ALT or AST $\geq 3 \times$ ULN and T-Bil $\geq 2 \times$ ULN
- ALT or AST $\geq 3 \times$ ULN associated with a clinical presentation suggestive of liver injury (ie, including the appearance of fatigue, nausea, vomiting, jaundice, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia)
- Serious hepatobiliary AE
- Severe hepatobiliary AE
- Hepatobiliary AE leading to discontinuation
- Any transaminase elevation associated with a clinical presentation suggestive of liver injury

- As elevation of ALT or AST ≥ 3 × ULN (without clinical presentation suggestive of liver injury)
- AE related to suicide (if there are any "yes" responses to any of the questions in the C-SSRS)

9.4. Adverse Event

9.4.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (International Council for Harmonisation [ICH] E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

Dizziness, somnolence, edema, and weight gain are defined as significant AE. Any other significant AEs to be added will be specified in the SAP.

It is the responsibility of Investigators, based on their knowledge and experience, to determine those circumstances or abnormal laboratory findings which should be considered AEs.

9.4.2. Serious Adverse Event

A SAE is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or
- Is an important medical event.

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples include allergic bronchospasm, convulsions, and blood dyscrasias or development of drug dependency or drug abuse.

Note:

- Procedures are not AEs or SAEs, but the reason for the procedure may be an AE or SAE.
- Pre-planned (prior to signing the ICF) procedures or treatments requiring hospitalizations for pre-existing conditions that do not worsen in severity are not SAEs.

9.4.3. Severity Assessment

The following definitions should be used to assess intensity of AEs:

- Mild: Awareness of sign or symptom, but easily tolerated, ie, does not interfere with subject's usual function.
- Moderate: Discomfort enough to cause interference with usual activity.
- Severe: Incapacitating with inability to work or do usual activity, ie, interferes significantly with subject's usual function.

Severity vs. Seriousness: Severity is used to describe the intensity of a specific event while the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "seriousness," which is based on patient/event outcome at the time of the event.

9.4.4. Causality Assessment

The Investigator should assess causal relationship between an AE and the study drug on the basis of his/her clinical judgment and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

  or

  - The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its chemical group, or is predicted by known pharmacology.
- Not Related:
  - The AE does not follow a reasonable sequence from study drug administration, or can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

9.4.5. Action Taken Regarding Study Drug(s)

- Dose Not Changed: No change in study drug dosage was made.
- Drug Withdrawn: The study drug was permanently stopped.
- Dose Reduced: The dosage of study drug was reduced.
- Drug Interrupted: The study drug was temporarily stopped.
- Not Applicable: Subject died, study treatment had been completed prior to reaction/event, or reaction/event occurred prior to start of treatment.

9.4.6. Other Action Taken for Event

- None.
  - No treatment was required.
- Medication required.
  - Prescription and/or OTC medication was required to treat the AE.
- Hospitalization or prolongation of hospitalization required.
  - Hospitalization was required or prolonged due to the AE, whether or not medication was required.
- Other.

9.4.7. Adverse Event Outcome

- Recovered/Resolved
  - The subject fully recovered from the AE with no residual effect observed.
- Recovering/Resolving
  - The AE improved but has not fully resolved.
- Not Recovered/Not Resolved
  - The AE itself is still present and observable.
- Recovered/Resolved with Sequelae
  - The residual effects of the AE are still present and observable.
  - Include sequelae/residual effects.
- Fatal
  - Fatal should be used when death is a direct outcome of the AE.
- Unknown

9.4.8. Definition of Adverse Drug Reaction

Those AEs for which the relationship to the investigational product is considered "Related" will be handled as adverse drug reactions (ADRs).

9.5. Serious Adverse Events and Adverse Event of Special Interest Reporting–Procedure For Investigators

All AEs, SAEs, and AESI, will be reported in the CRF.

The following types of events should be reported to the sponsor within 24 hours after becoming aware of the event in the designated form to the eCRF:

- SAEs (see Section 9.4.2 for definition)
- Increase in ALT or AST ≥ 5 × ULN
- ALT or AST rises to ≥ 3 × ULN and persists for more than 2 weeks
- Concurrent increases in ALT or AST ≥ 3 × ULN and T-Bil ≥ 2 × ULN
- ALT or AST ≥ 3 × ULN associated with a clinical presentation suggestive of liver injury (ie, including the appearance of fatigue, nausea, vomiting, jaundice, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia)
- AE related to suicide (if there are any "yes" responses to any of the questions in the C-SSRS)

The following types of events should be reported to the sponsor as promptly as possible after becoming aware of the event in the designated form to the eCRF:

- Severe hepatobiliary AE
- Hepatobiliary AE leading to discontinuation
- Any transaminase elevation associated with a clinical presentation suggestive of liver injury
- As elevation of ALT or AST ≥ 3 × ULN (without clinical presentation suggestive of liver injury)

All events (serious and non-serious) must be reported with Investigator's assessment of the event's seriousness, severity, and causality to the blinded study drug. A detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided. Specific or estimated dates of event onset, treatment, and resolution should be included when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed, and include the results if available. Source documents (including medical reports) will be retained at the study site and should not be submitted to the Sponsor for SAE reporting purposes.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

In the event that eCRF is unavailable, report SAEs/AESIs on a Serious Adverse Event Report (SAVER) form. All completed SAVER forms must be signed by the Investigator, and e-mailed to CMIC.

9.6. Notifying Regulatory Authorities, Investigators, and Institutional Review Board/Ethics Committee

Daiichi Sankyo and/or CMIC will inform Investigators, Institutional Review Boards/Ethics Committees (IRBs/ECs), and regulatory authorities of any suspected unexpected serious adverse reactions occurring in other study sites or other studies of the investigational drug, as appropriate per local reporting requirements. Daiichi Sankyo and/or CMIC will comply with any additional local safety reporting requirements. The section of "Reference Safety Information" in the updated investigator's brochure should be referred to judge "Unexpected".

9.7. Exposure In Utero During Clinical Studies

Daiichi Sankyo must be notified of any subject who becomes pregnant while receiving or at the time of discontinuing the study drug.

Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the Investigator, or designee, to report any pregnancy in a female subject or a male subject's female partner using the exposure in utero (EIU) reporting form. Please contact your study monitor to receive the EIU Reporting Form upon learning of a pregnancy. The Investigator should make every effort to follow the subject until completion of the pregnancy and complete the EIU Reporting Form with complete pregnancy outcome information, including normal delivery and induced abortion. The adverse pregnancy outcome, either serious or non-serious, should be reported in accordance with study procedures. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (ie, post-partum complications, spontaneous or induced abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the Investigator should follow the procedures for reporting SAEs outlined in Section 9.5.

9.8. Clinical Laboratory Evaluations

The study site staff will collect blood and urine specimens for routine laboratory tests at specified times. Specimens will be stored under conditions stipulated in the Sample Handling Manual until they are transported for measurement. Specimens will be transported and measured by a central laboratory.

Table 9.1 summarizes the laboratory parameters to be assessed and the times of assessment.

Results of all laboratory tests will be reported from the central laboratory to the site.

A value or finding that represents a clinically significant abnormal change should be regarded as an AE, and should be described (diagnosed) appropriately in the CRF.

Table 9.1: Laboratory Parameters to be Assessed, and Time of Assessment

	Parameters	**Time of assessment**
Hematology	WBC, RBC, hemoglobin, hematocrit, platelet count, differential leukocyte (neutrophil, eosinophil, basophil, monocyte, lymphocyte) counts, reticulocyte count	Visit 1, Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, Visit 8, Early Termination
Blood chemistry	Total protein, albumin, A/G ratio, T-Bil, AST (GOT), ALT (GPT), ALP, γ-GT (γ-GTP), LDH, BUN, creatinine, uric acid, creatine kinase, total cholesterol, triglycerides, Na, K, Cl, Ca, Mg, inorganic phosphorus, bicarbonate, CRP	
Urinalysis	Standard urinalysis, including microscopic examination Specific gravity, pH, protein, glucose, ketones, urobilinogen, occult blood, RBC, WBC, bilirubin	
HbA1c	HbA1c	Visit 2 and Visit 7, Early Termination
Pregnancy	Qualitative test (urine)	Visit 1 and Visit 7, Early Termination

In cases of liver laboratory abnormalities, it is important to ensure that the nature and the extent of liver injury is identified and study subjects are monitored until the liver laboratory assessments return to normal. Subjects who have any transaminase elevation associated with a clinical presentation suggestive of liver injury (ie, including the appearance of fatigue, nausea, vomiting, jaundice, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia) or an elevation of ALT or AST ≥ 3 × ULN (without clinical presentation suggestive of liver injury) at any visit should be monitored closely, according to the following:

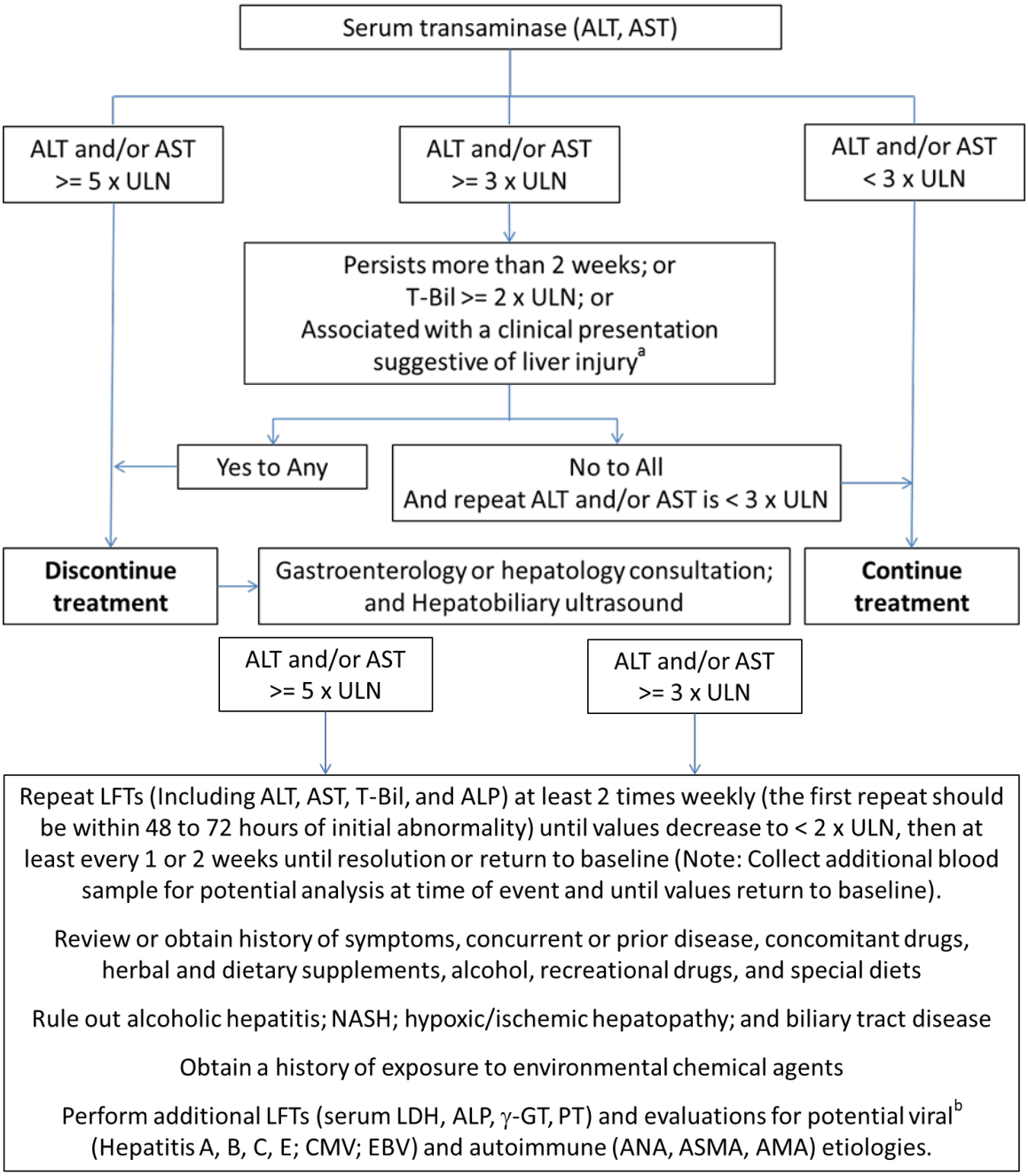
- Repeat liver tests of at least all four of the usual serum measures (ALT, AST, alkaline phosphatase [ALP]), and T-Bil at least 2 times weekly (the first repeat should be within 48 to 72 hours of initial abnormality) until values have decreased to < 2 × ULN, then at least every 1 or 2 weeks until resolution or return to baseline. An additional serum separating tube of blood will be collected at time of event and until values return to baseline. Samples will be stored for further analysis, as required.
- Review or obtain a detailed history of symptoms and prior or concurrent diseases.

- Review or obtain a history of the use of concomitant drugs, including nonprescription medications, herbal and dietary supplements, alcohol, recreational drugs, and special diets.
- Rule out alcoholic hepatitis; non-alcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtain a history of exposure to environmental chemical agents.
- Perform additional liver function tests (eg, serum lactate dehydrogenase, ALP, gamma-glutamyl transpeptidase, prothrombin time), evaluations for potential viral etiologies (including hepatitis A, B, C, E; cytomegalovirus; Epstein-Barr virus) and autoimmune etiologies (anti-nuclear antibody, anti-smooth muscle antibody, anti-mitochondrial antibody).

Combined elevations of aminotransferases and bilirubin meeting the criteria of a potential Hy's Law case [ALT or AST ≥ 3 × ULN with simultaneous T-Bil ≥ 2 × ULN], either serious or non-serious and whether or not causally related, should always be reported to the sponsor within 24 hours (refer to Section 9.2), with the investigator's assessment of seriousness, causality, and a detailed narrative. (Food Drug Administration's Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation; July 2009; http://www.fda.gov/downloads/Drugs/Guidance/UCM174090.pdf). These events should be reported as soon as possible following the procedures outlined in Section 9.5 for SAE reporting. Criteria for discontinuing subjects based on transaminase increases are provided in Section 5.7.1.

For subjects discontinued from the study due to any transaminase increase or hepatic event, the following should be performed:

- Gastroenterology or hepatology consultation
- Hepatobiliary ultrasound



a: ie, including the appearance of fatigue, nausea, vomiting, jaundice, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia
b: Evaluations for potential viral etiologies will include: Hep A Ab by IgM acute, HBsAg, HBeAg, anti-HBc, Hep C Ab, Hep C RNA by PCR , Hep E IgG Ab , Hep E IgM Ab, EBV IgG Ab, EBV IgM Ab, and CMV DNA by PCR
Abbreviations: ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase; CMV = cytomegalovirus, EBV = Epstein-Barr virus, γ-GT = gammaglutamyltransferase, LDH = lactate dehydrogenase, LFT = liver function test, PT = prothrombin time, ULN = upper limit of normal

9.9. Vital Signs

Vital signs will be recorded at all visits and will include pulse rate and blood pressure in a supine position in principle. For measurement of supine blood pressure, subjects should

be in a supine or semirecumbent position for a minimum of 5 minutes before the blood pressure measurement. Measurement of blood pressure should be conducted using a calibrated manometer or automatic inflatable cuff monitor. Results will be recorded in the CRF.

9.10. Electrocardiograms

At the stipulated times (Visit 1 and Visit 7), 12-lead ECG will be performed. Results (Normal/Abnormal, not clinically significant/Abnormal, clinically significant) will be recorded in the CRF.

9.11. Physical Findings

9.11.1. Body Height and Weight

At Screening (Visit 1), body height will be measured. Body weight will be measured at each visit. Results will be recorded in the CRF.

9.11.2. Medical Interview

Medical interview will be performed at each visit. Results will be recorded in the CRF.

9.11.3. Evaluation of Edema

At Visit 1 and Visit 7, evaluation of edema will be performed including medical interview and pitting. Results (presence or absence of edema and expression site) will be recorded in the CRF.

9.12. Other Examinations

9.12.1. Columbia-Suicide Severity Rating Scale[23]

The C-SSRS is a tool designed to systematically assess and track suicidal AEs (behavior and ideation). The C-SSRS assesses lifetime suicidality during an initial baseline evaluation using standardized questions, and then prospectively monitors ideations and behaviors at subsequent follow-up assessments throughout the trial. The reviewer is an investigator, sub-investigator or clinical study coordinator who has completed training prior to the study using the training material. The C-SSRS will be administered by the reviewer at each visit. Answers to all relevant questions will be recorded in the CRF. If the subject is judged to have suicidal behavior and/or suicidal ideation, appropriate measures will be implemented such as referring the subject to a specialist as described in the withdrawal procedures (see Section 5.7.3).

9.12.2. Hospital Anxiety and Depression Scale[18]

At each visit, subjects will provide a self-assessment using the HADS. The HADS consists of 7 items to score depression (4-point scale) and 7 items to score anxiety (4-point scale). The subject will respond to each item on the questionnaire. Based on the results, the investigator will check for the presence or absence of depression and/or anxiety. If the

subject is judged to have an AE, appropriate measures will be implemented such as referring the subject to a specialist. Result will be recorded in the CRF.

9.12.3. Pregnancy Test

Pregnancy tests (urine tests) will be conducted at the stipulated times (Visit 1 and Visit 7), for women of child-bearing potential only. All female subjects will be considered as women of child-bearing potential unless they have undergone surgical sterilization (with documented bilateral oophorectomy) or are postmenopausal and have experienced no menses within the previous 6 months. The subject is considered to be postmenopausal when 12 consecutive months of absence of menstruation is confirmed with no pathological or physiological factors. Results will be recorded in the CRF.

10. OTHER ASSESSMENTS

Not Applicable.

11. STATISTICAL METHODS

11.1. General Statistical Considerations

The modified intent-to-treat (mITT) analysis set will be used as primary efficacy analysis set for all efficacy analyses and the per-protocol set (PPS) will be used as supplementary analysis. All safety analyses will be conducted for the safety analysis set and, respectively. Patients with CLcr ≥60 mL and 30 to < 60 mL/min will be merged and analyzed.

The primary imputation will be based on “nonfuture dependence" model using the pattern mixture approach under the missing not at random (MNAR) mechanism for the missing weekly ADPS.[26], [27] Reason for dropout together with the time of dropout will be used for constructing the missing data pattern. Detail will be at Section 11.4.1 and in the SAP.

Missing weekly ADPS after the discontinuation will be imputed using multiple imputation (MI) method, and pattern mixture model (PMM) with different shift parameters depending on the reason for discontinuation (AE, LOE, or the others) will be used in the MI to impose penalty (ie, bad score) on the imputed weekly ADPS.

Intercurrent event of this study is treatment discontinuation. In order to supplement the pain score when continuing with no administration after this situation, the above imputation method was adopted.

Raw data will be presented to the exact precision at which they were collected.

For summary statistics, means and medians will be displayed to one more decimal place than was determined for raw data, dispersion statistics will have two more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as the raw data.

Quantitative data will be tabulated with descriptive summary statistics: arithmetic mean, standard deviation (SD), median, minimum and maximum values, and number of observations. For categorical data, frequency tables will be provided.

All hypothesis testing will provide the *P* values and their corresponding two-sided 95% confidence intervals if applicable. The significance level is 0.05 (two-sided) for all hypothesis testing. No adjustment for multiple comparisons will be made for all analyses.

Analysis for the change from baseline, including the shift table, will be conducted for the subjects who have an available baseline value and at least one post-randomization value.

Subgroup analyses will be pre-specified in the SAP.

11.2. Analysis Sets

All enrolled subjects will include all subjects who sign the ICF.

All randomized subjects will include all subjects who signed the ICF and were randomized.

The safety analysis set will include all subjects who signed the ICF and received at least one dose of study medication.

The mITT analysis set, primary analysis set for the efficacy analyses, will include all randomized subjects who received at least one dose of study medication.

The PPS will include all randomized subjects who received at least one dose of study medication, and who were sufficiently compliant with the protocol. The PPS will be used for supplementary analyses.

11.3. Study Population Data

The number of enrolled subjects and randomized subjects will be summarized. The number and percentage will be tabulated for subjects who completed the study, prematurely discontinued from the study, and the reason for the study discontinuation. In addition, the number and percentage of subjects for each analysis set will be tabulated.

Demographic and baseline characteristics will be summarized for the randomized subjects, the safety analysis set, mITT analysis set, and PPS.

Treatment compliance for each subject will be summarized.

11.4. Efficacy Analyses

The mITT analysis set will be used for all efficacy analyses and the PPS will be only for the primary efficacy analysis described in Section 11.4.1 as supplementary analysis. All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance and all confidence intervals (CIs) will be 2-sided 95% CIs, unless stated otherwise.

11.4.1. Primary Efficacy Analyses

Missing weekly ADPS will be imputed using a MI method. In the MI method, a PMM under the assumption of nonfuture dependence.[26], [27], which has different shift parameters depending on the reason for discontinuation (AE, LOE, or any other reasons), will be used to impose penalty (ie, bad score) on the weekly ADPS. This imputation is based on a MNAR mechanism for missing weekly ADPS.

In the MI step, Markov Chain Monte Carlo (MCMC) with relevant covariates (specified in the SAP) will be used to generate a monotone missing pattern. Subsequently, Regression with Predictive Mean Matching (REGPMM) with the same covariates as the MCMC above was applied to the monotone missing pattern data to impute all missing weekly ADPS for completed datasets. In the REGPMM step, the following shifting amount will be put on the imputed weekly ADPS at the first missing week for each subjects:

1.0*residual standard deviation (RSD)*U(0.1) for subjects who discontinued due to AE

1.0*RSD*U(0,1) for subjects who discontinued due to LOE

0.5*RSD*U(0,1) for subjects who discontinued due to any other reasons

where the coefficients (1.0, 1.0, 0.5) are shifting parameter to impose different penalty depending on the reason for discontinuation, RSD is a RSD at the week which will be estimated using a regression model in the REGPMM step, and U(0,1) is a random variable from a uniform distribution with a range of 0 to 1.

For subjects who completed the study but had missing weekly ADPS, the missing weekly ADPS will be imputed under the missing at random mechanism.

The imputed weekly ADPS which is greater than 10 will be replaced with 10 (theoretical maximal value for weekly ADPS). Additionally, regarding the subjects who discontinued due to LOE, the imputed weekly ADPS which is lower than the baseline ADPS for the corresponding subject will be replaced with the baseline ADPS for the subject.

Each complete dataset will be analyzed using the ANCOVA with treatment as fixed effects and baseline ADPS as covariate to compare the change from baseline in weekly ADPS at Week 14 between mirogabalin and placebo. The results will be combined using Rubin's rule.

Sensitivity analysis for the primary endpoint includes the followings:

- The primary analysis on the mITT analysis set using "nonfuture dependence" MNAR model[26, 27] with different shift parameters including (3, 3, 1.5), (5, 5, 2.5), and (0, 0, 0).

Supplementary analysis for the primary endpoint includes the followings:

- The primary analysis on the mITT analysis set using placebo multiple imputation
- ANCOVA with baseline ADPS and treatment as covariates on the mITT analysis set using baseline observation carried forward
- ANCOVA with baseline ADPS and treatment as covariates on the mITT analysis set using last observation carried forward
- The primary analysis on the PPS using "nonfuture dependence" MNAR model with the shift parameters of (1, 1, 0.5).

11.4.2. Secondary Efficacy Analyses

For all secondary efficacy analyses, the summary statistics or frequency tables will be created for values in the parameters and changes from baseline (if applicable) by treatment group and scheduled visit/week.

11.4.2.1. Key Secondary Efficacy Analyses

11.4.2.1.1. ADPS Responder Rate

ADPS responder rate, defined as the proportion of subjects with ≥ 30%, and ≥ 50% reduction from baseline to Week 14, will be calculated by treatment group. ADPS responder rate of each arm of DS-5565 will be compared with that of placebo using logistic regression model. The cumulative distribution of reduction from baseline in ADPS will be provided as a continuous responder analysis.

The cumulative distribution of reduction from the baseline in weekly ADPS at Week 14 will be graphically displayed.

11.4.2.1.2. Short-Form McGill Pain Questionnaire

For the sensory score, affective score, total score, VAS, and the present pain intensity index, the measured value and the change from baseline will be summarized at each scheduled visit. The change from baseline in the parameters above will be compared between each arm of mirogabalin and placebo.

11.4.2.1.3. Sleep-interference Score

The summary statistics will be computed for the ADSIS and their change from baseline at each week. The change from baseline in sleep interference score will be compared between each arm of mirogabalin and placebo.

11.4.2.1.4. Patient Global Impression of Change

The PGIC responder rates of much improved or better (ie, score$\leq$ 2) for the mirogabalin will be compared with that for the placebo. The same analysis will be repeated for the PGIC responder rate of minimally improved or better (ie, score $\leq$ 3).

11.4.2.1.5. Medical Outcomes Study Sleep Scale

For the subscales of sleep disturbance, snoring, awakening short of breath or with a headache, somnolence, sleep adequacy, sleep problems index, and quantity of sleep, the change from baseline in the subscales will be compared between the mirogabalin and the placebo. The optimal sleep which is dichotomized version of optimal sleep findings, the summary will be provided as frequency tables and the parameter will also be compared between the mirogabalin and the placebo.

11.4.2.1.6. Hospital Anxiety and Depression Scale

The change from baseline in the subscales of Anxiety and Depression will be compared between the mirogabalin and the placebo.

11.4.2.1.7. Neuropathic Pain Symptom Inventory

For the sub-total score of each dimension (spontaneous ongoing pain, spontaneous paroxysmal pain, evoked pain, and paresthesia/dysesthesia) and total score, the change from baseline will be compared between the mirogabalin and the placebo.

11.4.2.1.8. EQ-5D-5L

The change from baseline in the converted single index value will be compared between the mirogabalin and the placebo. The change from baseline in VAS will be also compared between the treatments.

11.4.2.1.9. Spinal Cord Independence Measure

For the sub-total score of each category (self-care, respiration and sphincter management, and mobility) and the total score, the change from baseline will be compared between the mirogabalin and the placebo.

11.4.2.1.10. Evaluation of allodynia

The change from baseline in of allodynia will be compared between each arm of mirogabalin and placebo.

11.4.2.2. Other Secondary Efficacy Analyses

Not Applicable.

11.4.3. Exploratory Efficacy Analyses

Detail procedures for exploratory efficacy analysis are specified in SAP, etc.

11.4.4. Pharmacokinetic/Pharmacodynamic/Biomarker Analyses

Not Applicable.

11.4.5. Safety Analyses

All safety analyses will be performed using the safety analysis set.

11.4.5.1. Adverse Event Analyses

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs are defined as AEs that newly emerges or worsen in severity after the first administration of the study drug until the following dates:

- Follow-up visit for the subjects who did not participate in the open-label extension study.
- 14 days after the last dose of study drug in the double-blind study or the first dose of study drug in the open-label extension study whichever is earlier for the subjects who participated in the open-label extension study.

The number and percentage of subjects reporting TEAE and treatment-emergent ADR (TEADR) will be calculated overall, by system organ class (SOC), and by preferred term (PT). TEAE and TEADR will be further summarized by SOC, PT, and severity and by SOC, PT, and relationship to study drug. Similarly, the number and percentage of subjects with serious TEAE, serious TEADR, significant TEAE, significant TEADR, TEAE leading to treatment discontinuation, and TEADR leading to treatment discontinuation will be tabulated.

Time to first dizziness and somnolence, defined as the duration from first administration of investigational product to the first TEAE, will be summarized based on the Kaplan-Meier product limit method.

11.4.5.2. Clinical Laboratory Evaluation Analyses

Summary statistics will be provided for the measured value and change from baseline in the clinical laboratory tests results by scheduled visit. Shift table will be created for the categorical data (eg, abnormal low, normal, abnormal high") between baseline and each scheduled visit of evaluation.

Additionally, for ALT, AST, T-Bil, and ALP, the number and percentage of subjects who meet the criteria specified in Food Drug Administration Drug-Induced Liver Injury guideline[24] will be tabulated and evaluation of drug-induced serious hepatotoxicity plot will also be provided.

11.4.5.3. Vital Sign Analyses

Summary statistics will be provided for measured value and change from baseline in vital signs parameters by scheduled visit.

11.4.5.4. Electrocardiogram Analyses

Shift table will be provided for ECG parameters between baseline and visit of End of Treatment/Early Termination.

11.4.5.5. Physical Findings

Summary statistics will be calculated for the measured value and change from baseline in body weight measurements by scheduled. The number and percentage of subjects who increased their body weight by 5% or 10% from the baseline will be also tabulated.

For the evaluation of edema, the results (presence or absence) will be tabulated for each expression site.

11.4.5.6. Columbia-Suicide Severity Rating Scale

The results from C-SSRS will be tabulated.

11.4.5.7. Hospital Anxiety and Depression Scale

The subscales of Anxiety and Depression for HADS will be summarized by scheduled visit.

11.4.6. Other Endpoint Analysis

Not Applicable.

11.5. Interim Analyses

Not Applicable

11.6. Sample Size Determination

A total of 274 subjects will be randomized to one of the placebo-arm and mirogabalin-arm with randomization ratio of 1:1.

We assumed normal distributions with common SD for the change from baseline in ADPS at Week 14 in placebo and mirogabalin arms. Applying Student's t-test with one-sided significant level of 0.025, a total of 270 subjects (135 subjects for each arm) is required to provide 80% statistical power under the assumption of 0.6 difference (vs. placebo) and common SD of 1.75 for the change from baseline in ADPS at Week 14. The treatment difference and common SD are assumed as expected values from the results of Asian Phase 3 studies for DPNP patients (DS5565-A-J303) and PHN patients (DS5565-A-J304). As a primary analysis set for the efficacy is a mITT analysis set defined as subjects who were randomized and received at least one dose of study drug, we planned 274 subjects to be randomized to consider dropouts from the randomization to the first administration of the study drug.

11.7. Statistical Analysis Process

The SAP will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other clinical study information such as subject disposition, demographic and baseline characteristics, study drug exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused, and spurious data will be addressed.

The SAP will be finalized prior to unblinding to preserve the integrity of the statistical analysis and clinical study conclusions. A change in the planned statistical analysis will require a protocol amendment only if it substantively alters the principal features of the protocol. Any deviations from the planned statistical analyses in the protocol will be fully described in the SAP.

All statistical analyses will be performed using Statistical Analysis System (SAS)® Version 9.3 or higher (SAS Institute, Cary, NC 27513).

12. DATA INTEGRITY AND QUALITY ASSURANCE

12.1. Monitoring and Inspections

The study monitors and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (eg, CRFs, source data, and other pertinent documents).

The verification of adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH GCP and local regulations on the conduct of clinical research will be accomplished through a combination of onsite visits by the study monitors and review of study data remotely. The frequency of the monitoring visit will vary based on the activity at each study site. The monitors are responsible for inspecting the CRFs and ensuring completeness of the study essential documents. The monitors should have access to subject medical records and other study-related records needed to verify the entries on the CRFs. Detailed information is provided in the monitoring plan.

The monitors will communicate deviations from the protocol, SOPs, GCP and applicable regulations to the Investigator and will ensure that appropriate action (s) designed to prevent recurrence of the detected deviations is taken and documented.

The Investigator agrees to cooperate with the study monitors to ensure that any problems detected in the course of these monitoring visits are addressed to the satisfaction of the sponsor and documented.

In accordance with ICH GCP and the Sponsor's audit plans, this study site may be selected for audit by representatives from the Sponsor. Audit of study site facilities (eg, pharmacy, drug storage areas, laboratories) and review of study related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements. The Investigator should respond to audit findings. In the event that a regulatory authority informs the Investigator that it intends to conduct an inspection, the Sponsor shall be notified immediately.

12.2. Data Collection

Daiichi Sankyo will supply eCRFs. An eCRF must be completed for each subject who signs an ICF and undergoes any screening procedure. If a subject is not treated, the reason must be recorded on the eCRF. All data collected during the study will be recorded in this individual, subject-specific eCRF. Instructions will be provided for the completion of the eCRF and any corrections made will be automatically documented via the electronic data capture (EDC) software's "audit trail."

Completion of the eCRF should be kept current to enable the monitor to review the subject's status throughout the course of the study. All information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood. The eCRF will be completed, reviewed and signed off or e-signed by the Investigator. The Investigator will sign and date the indicated places on the eCRF via the EDC system's electronic signature. These signatures will indicate that the Investigator

inspected or reviewed the data on the eCRF, the data queries, and the site notifications, and agrees with the content.

12.3. Data Management

Each subject will be identified in the database by a unique subject identifier as defined by the sponsor.

To ensure the quality of clinical data across all subjects and study sites, a Clinical Data Management review will be performed on subject data according to specifications given to Daiichi Sankyo. Data will be vetted both electronically and manually for CRFs and the data will be electronically vetted by programmed data rules within the application. Queries generated by rules and raised by reviewers will be generated within the EDC application. During this review, subject data will be checked for consistency, completeness and any apparent discrepancies.

Data received from external sources such as central laboratories will be reconciled to the clinical database.

SAEs in the clinical database will be reconciled with the safety database.

All AEs will be coded using MedDRA. Concomitant medication will be coded using WHO drug.

Data that may potentially unblind the treatment assignment (ie, treatment allocation, and study drug preparation/accountability data) will be handled with special care during the data cleaning and review process. These data will be handled in such a way that, prior to unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to quality assurance representatives for the purposes of conducting independent audits.

12.4. Study Documentation and Storage

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, X-rays, and correspondence.

Records of subjects, source documents, monitoring visit logs, data correction forms, CRFs, inventory of study drug, regulatory documents (eg, protocol and amendments, IRB/EC correspondence and approvals, approved and signed ICFs, Investigator's Agreement, clinical supplies receipts, distribution and return records), and other sponsor correspondence pertaining to the study must be kept in appropriate study files at the study site (Trial Master File). Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records will be retained in a secure file for the period required by the institution or study site policy. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

12.5. Record Keeping

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system (Trial Master File) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Essential documents contained in the Trial Master File include:

- Subject files containing completed CRFs, ICFs, and supporting copies of source documentation (if kept).
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the EC/IRB and the Sponsor.
- Records related to the study drug(s) including acknowledgment of receipt at study site, accountability records and final reconciliation and applicable correspondence.

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

All study related essential documentation will be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have lapsed since the formal discontinuation of clinical development of the investigational drug. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

Subject's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

No study document should be destroyed without prior written agreement between Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify Sponsor in writing of the new responsible person and/or the new location.

13. FINANCING AND INSURANCE

13.1. Finances

Prior to starting the study, the Principal Investigator and/or institution will sign a clinical study agreement with Daiichi Sankyo and/or the contract research organization (CRO). This agreement will include the financial information agreed upon by the parties.

13.2. Reimbursement, Indemnity, and Insurance

The Sponsor provides insurance for study subjects to make available compensation in case of study-related injury.

Reimbursement, indemnity and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

14. PUBLICATION POLICY AND PUBLIC DISCLOSURE OF CLINICAL TRIAL INFORMATION

Daiichi Sankyo. is committed to meeting the highest standards of publication and public disclosure of information arising from clinical trials sponsored by the company. We will comply with US, EU, and Japanese policies for public disclosure of the clinical trial protocol and clinical trial results, and for sharing of clinical trial data. We follow the principles set forward in "Good Publication Practice for Communicating Company-Sponsored Medical Research", and publications will adhere to the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" established by the International Council of Medical Journal Editors.

In order to ensure that we are in compliance with the public disclosure policies and the International Council of Medical Journal Editors recommendations, and to protect proprietary information generated during the study, all publications (manuscripts, abstracts, or other public disclosure) based on data generated in this study must be accepted, reviewed, and approved in writing by the sponsor prior to submission.

15. ETHICS AND STUDY ADMINISTRATIVE INFORMATION

15.1. Compliance Statement, Ethics, and Regulatory Compliance

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the ICH consolidated Guideline E6 for GCP (CPMP/ICH/135/95), and applicable regulatory requirement(s).

15.2. Subject Confidentiality

The Investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations.

The Investigator must ensure that the subject's anonymity is maintained. On the CRFs or other documents submitted to the Sponsor or the CRO, subjects should be identified by a unique subject identifier as designated by the Sponsor. Documents that are not for submission to the Sponsor or the CRO (eg, signed ICF) should be kept in strict confidence by the Investigator.

In compliance with ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/EC direct access to review the subject's original medical records for verification of study-related procedures and data. The Investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above named representatives without violating the confidentiality of the subject.

15.3. Informed Consent

Before a subject's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific procedures or any study drugs are administered. Subjects should be given the opportunity to ask questions and receive satisfactory answers to their inquiries, and should have adequate time to decide whether or not to participate in the study. The written ICF should be prepared in the local language(s) of the potential subject population.

In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form and any revision(s) should be approved by the EC or IRB prior to being provided to potential subjects.

The subject's written informed consent should be documented in the subject's medical records. The ICF should be signed and personally dated by the subject and by the person who conducted the informed consent discussion (not necessarily the Investigator). The original signed ICF should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject. The date and time (if applicable) that informed consent was given should be recorded on the CRF.

If the subject cannot sign by him/herself due to paralysis of spinal cord injury, the ICH-GCP Section 4.8.9, and impartial witness should be present during the entire informed

consent discussion. This witness should sign the ICF. By signing ICF, the witness attests that the information in the ICF and any other written information was adequately explained to and apparently understood by the subject and the informed consent was freely given by the subject.

Suggested model text for the ICF for the study are provided in the Sponsor's ICF template for the Investigator to prepare the documents to be used at his or her study site. Updates to applicable forms will be communicated via letter from the Sponsor.

15.4. Regulatory Compliance

The study protocol, subject information and consent form, the Investigator Brochure, any subject written instructions to be given to the subject, available safety information, subject recruitment procedures (eg, advertisements), information about payments and compensation available to the subjects, and documentation evidencing the Investigator's qualifications should be submitted to the EC or IRB for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the SAP.

The Sponsor will appoint a Coordinating Investigator. Among other possible duties, the Coordinating Investigator will be responsible for testifying to the accuracy of the description of the study conduct. Because the Coordinating Investigator should have personal knowledge of the conduct of the study, he or she will normally be chosen from among those Investigators who have enrolled and treated at least one subject. However, where an Investigator has special knowledge of the field or of the trial, the Coordinating Investigator can be chosen prior to enrollment of the first subject. In all cases, the Coordinating Investigator must be chosen prior to locking the database.

The Investigator must submit and, where necessary, obtain approval from the EC or IRB for all subsequent protocol amendments and changes to the ICF. The Investigator should notify the EC or IRB of deviations from the protocol or SAEs occurring at the study site and other AE reports received from the Sponsor/CRO, in accordance with local procedures.

As required by local regulations, the Sponsor's local Regulatory Affairs group or representative to whom this responsibility has been delegated will ensure all legal aspects are covered, and approval from the appropriate regulatory bodies obtained, prior to study initiation. If changes to the initial protocol and other relevant study documents are made, this representative will also ensure that any revised documents required for submission are submitted to regulatory authorities and implementation of these changes happen only after approval by the relevant regulatory bodies.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Regulatory Authority(ies) in any area of the world, or if the Investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational drug, the Sponsor should be informed immediately.

In addition, the Investigator will inform the Sponsor immediately of any urgent safety measures taken by the Investigator to protect the study subjects against any immediate hazard, and of any suspected/actual serious GCP non-compliance that the Investigator becomes aware of.

15.5. Protocol Deviations

The Investigator should conduct the study in compliance with the protocol agreed to by Sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRBs/ECs.

A deviation to any protocol procedure or waiver to any stated criteria will not be allowed in this study except where necessary to eliminate immediate hazard(s) to the subject. Sponsor must be notified of all intended or unintended deviations to the protocol (eg, inclusion/exclusion criteria, dosing, missed study visits) on an expedited basis.

The Investigator, or person designated by the Investigator, should document and explain any deviation from the approved protocol.

If a subject was ineligible or received the incorrect dose or study treatment, and had at least 1 administration of study drug, data should be collected for safety purposes.

If applicable, the Investigator should notify the IRB of deviations from the protocol in accordance with local procedures.

15.6. Supply of New Information Affecting the Conduct of the Study

When new information becomes available that may adversely affect the safety of subjects or the conduct of the study, the Sponsor will inform all Investigators involved in the clinical study, ECs/IRBs, and regulatory authorities of such information, and when needed, will amend the protocol and/or subject information.

The Investigator should immediately inform the subject whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue participation in the study. The communication should be documented on medical records, for example, and it should be confirmed whether the subject is willing to remain in the study.

If the subject information is revised, it must be re-approved by the IEC/IRB. The Investigator should obtain written informed consent to continue participation with the revised written information even if subjects were already informed of the relevant information. The Investigator or other responsible personnel who provided explanations and the subject should sign and date the revised ICF.

15.7. Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be communicated to the Investigator by Daiichi Sankyo or the CRO. Also, the Sponsor will ensure the timely submission of amendments to regulatory authorities.

A global protocol amendment will affect study conduct at all study site s in all regions of the world. Such amendments will be incorporated into a revised protocol document. Changes made by such amendments will be documented in a Summary of Changes document. These protocol amendments will undergo the same review and approval process as the original protocol.

A local protocol amendment will affect study conduct at a particular study site(s) and/or in a particular region/country. Sponsor approval of local amendments will be clearly documented.

A protocol amendment may be implemented after it has been approved by the IRB/EC and, unless immediate implementation of the change is necessary for subject safety.

15.8. Study Termination

The sponsor will immediately suspend part of the study or the entire study if any of the following events makes the sponsor consider it difficult to continue the study:

1. Any new safety or SAE information becomes available on the investigational products.
2. The sponsor, the study site, or the investigator has implemented any significant GCP non-compliance or any significant protocol deviation.
3. Any other information is obtained during the study.

The sponsor will decide on whether to prematurely terminate part of the study or the entire study and will document the decision.

If the sponsor decides to prematurely terminate part of the study or the entire study after consulting with medical experts and other designated people, the sponsor will promptly notify the study site and the investigator in writing of termination and the reason for the action. If the study is prematurely terminated or suspended for any reason, the investigator will promptly inform the subjects participating in the study and will provide appropriate treatments and follow-up for the subjects to confirm their safety.

15.9. Data and Safety Monitoring Board

Not Applicable.

15.10. Address List

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17. APPENDICES

17.1. Schedule of Events

Table 17.1: Study Visit

		Screening	Randomization	Treatment period				End of Treatment	Post-treatment follow-up[a]	Early Termination
Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Week		**−1**	**0**	**1**	**2**	**6**	**10**	**14**	**15**	
Day		**≤ −7**	**1**	**8**	**15**	**43**	**71**	**99**	**Day 7 post-last-dose**	
Visit window (days)		**−7 to −14**	**-**	**6 to 10**	**13 to 17**	**40 to 46**	**68 to 74**	**96 to 102**	**Day 5 to 14 post-last-dose**	
Informed consent		X[b]								
Inclusion/exclusion criteria		X	X							
Demographic information		X								
Medical/surgical history		X								
Evaluation of ASIA Impairment		X						X		X
Efficacy parameter(s) - see next table		X	X	X	X	X	X	X		X
Body height and weight		X	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]
Medical interview[d]		X	X	X	X	X	X	X	X	X
Evaluation of edema		X						X		X
Vital signs[e]		X	X	X	X	X	X	X	X	X
12-lead ECG		X						X		X
Clinical safety laboratory tests		X	X	X	X	X	X	X	X	X
C-SSRS		X	X	X	X	X	X	X	X	X
HADS		X	X	X	X	X	X	X	X	X
Pregnancy test		X						X		X
AE reporting	Non-serious AE		←	—	—	—	—	—	—	→
	SAE	←	—	—	—	—	—	—	—	→
Prior and concomitant medication		X	X	X	X	X	X	X	X	X
Investigational product dispensing			X	X	X	X	X			
Investigational product compliance				X	X	X	X	X		X

a: Follow-up observation is not required for patients who are enrolled in open-label extension study.
b: After informed consent is obtained, patients who are under treatment with the prohibited concomitant medications will undergo a washout period of 28 days or more.
c: Body weight only.
d: Check subject's health condition through verbal communication. Additional tests may be performed based on any signs or symptoms exhibited by subject.
e: For blood pressure, supine in principle.

Table 17.2: Efficacy Assessment by Visit

	Screening	Randomization	Treatment period				End of Treatment	Post-treatment follow-up	Early Termination
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Week	**−1**	**0**	**1**	**2**	**6**	**10**	**14**	**15**	
Day	**≤ −7**	**1**	**8**	**15**	**43**	**71**	**99**	**Day 7 post-last-dose**	
Visit window (days)	**−7 to −14**	**-**	**6 to 10**	**13 to 17**	**40 to 46**	**68 to 74**	**96 to 102**	**Day 5 to 14 post-last-dose**	
Pain diaries	←	—	—	—	—	—	→		
Sleep interference diaries	←	—	—	—	—	—	→		
Short-Form McGill Pain Questionnaire	X	X	X	X	X	X	X		X
Medical Outcome Study sleep scale		X					X		X
Patient Global Impression of Change							X		X
Neuropathic Pain Symptom Inventory		X					X		X
EQ-5D-5L		X					X		X
Hospital Anxiety and Depression Scale		X					X		X
Spinal Cord Independence Measure		X					X		X
Evaluation of allodynia		X					X		X
Bladder diaries[a]	←	→				←	→		
Overactive Bladder Symptom Score[a]	X						X		X

a: For only Japanese subjects with self-urination, and who gave informed consent for overactive bladder evaluation and meet the diagnostic criteria of overactive bladder in OAB-SS at Visit 1 (As for Overactive Bladder Symptom Score in Visit 1, for only Japanese subjects with self-urination)