CLINICAL STUDY PROTOCOL

A JAPANESE, PHASE 3, OPEN-LABEL, 14-WEEK STUDY OF DS-5565 IN PATIENTS WITH PAIN ASSOCIATED WITH DIABETIC PERIPHERAL NEUROPATHY WITH RENAL IMPAIRMENT OR POST-HERPETIC NEURALGIA WITH RENAL IMPAIRMENT

DS5565-A-J313

VERSION 1.0, 13 Oct 2015

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DAIICHI SANKYO

IMPORTANT STUDY ADMINISTRATIVE INFORMATION

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INVESTIGATOR AGREEMENT

A JAPANESE, PHASE 3, OPEN-LABEL, 14-WEEK STUDY OF DS-5565 IN PATIENTS WITH PAIN ASSOCIATED WITH DIABETIC PERIPHERAL NEUROPATHY WITH RENAL IMPAIRMENT OR POST-HERPETIC NEURALGIA WITH RENAL IMPAIRMENT

Sponsor Approval:

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

PPD	PPD
Print Name / Signature	**Print Name / Signature**
Vice President, Clinical Development Department, Daiichi Sankyo Co., Ltd	Clinical Study Lead, Clinical Development Department, Daiichi Sankyo Co., Ltd
Title	**Title**
Date (DD MMM YYYY)	**Date (DD MMM YYYY)**

Investigator's Signature:

I have fully discussed the objectives of this study and the contents of this protocol with a 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 Conference on 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

Protocol Number:	DS5565-A-J313
Investigational Product:	DS-5565
Active Ingredient(s)/INN:	Mirogabalin
Study Title:	A Japanese, phase 3, open-label, 14-week study of DS-5565 in patients with pain associated with diabetic peripheral neuropathy (DPNP) with renal impairment or post-herpetic neuralgia (PHN) with renal impairment
Study Phase:	Phase 3
Indication Under Investigation:	DPNP or PHN
Study Objectives:	Primary objective: To characterise the safety and tolerability of DS-5565 in subjects with moderate to severe renal impairment Secondary objectives: • To evaluate the effect of DS-5565 on the Average Daily Pain Score (ADPS) • To evaluate the ADPS responder rate (the proportion of subjects with ≥ 30% and ≥ 50% reduction from baseline to Week 14) • To evaluate the effect of DS-5565 on pain questionnaire, using the Short-Form McGill Pain Questionnaire ([SF-MPQ]: sensory, affective and total subscales, Visual Analog Scale, and present pain intensity) • To assess the effect of DS-5565 on sleep and patient impressions in pain • To evaluate pharmacokinetic of DS-5565
Study Design:	Multicenter, single-arm, open-label study The total 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 subjects will enter the titration period. For subjects with moderate renal impairment (creatinine clearance [CrCL]: 30-59 mL/min), the titration period will be applied at the first week of 2.5 mg *bis in die* (BID), and at the second week of 5 mg

	BID. After the titration period, the drug will be administered for 12 weeks of 7.5 mg BID. For subjects with severe renal impairment (CrCL: 15-29 mL/min), the titration period will be applied at the first week of 2.5 mg *quaque die* (QD), and at the second week of 5 mg QD. After the titration period, the drug will be administered for 12 weeks of 7.5 mg QD. For subjects with DPNP, any subjects who have been taking prohibited concomitant drugs will undergo a washout period of 7 days or more, prior to the screening. For subjects with PHN, any subjects who have been taking prohibited concomitant drugs or receiving prohibited concomitant therapy will undergo a washout period of 7 days or more, prior to the screening.
Study Duration (from FPI to LPLV):	January 2016 to May 2017
Study Sites and Location:	Approximately 35 study sites in Japan
Planned Sample Size:	Approximately 35 subjects will be enrolled in the study.
Subject Eligibility Criteria:	Inclusion Criteria: Subjects must satisfy all of the following criteria to be included in the study. For patients with DPNP and patients with PHN: 1) Age ≥ 20 years at informed consent 2) Able to give written informed consent for study participation, understand procedures of this study, and complete patient-reported questionnaires adequately 3) CrCL (using the Cockcroft-Gault equation): 15-59 mL/min at screening 4) At screening, a pain scale of ≥ 40 mm on VAS of SF-MPQ 5) At initiation of study treatment, 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) For patients with DPNP only: 6) Type 1 or type 2 diabetes mellitus at screening 7) Painful distal symmetric polyneuropathy, diagnosed at least 6 months prior to screening (see Procedures manual for the Diagnosis of Diabetic Peripheral Neuropathy and

	Neurological Examination for details) For patients with PHN only: 8) PHN defined as pain present for 3 months or more after herpes zoster skin rash at screening Exclusion Criteria: Subjects who meet any of the following criteria will be excluded from participation in the study. For patients with DPNP and patients with PHN: 1) At screening, a pain scale of ≥ 90 mm on VAS of SF-MPQ 2) At initiation of study treatment, a pain scale of ≥ 90 mm on VAS of SF-MPQ, or at least a daily pain score of ≥ 9 during observation period 3) Major psychiatric disorders at screening or initiation of study treatment 4) Use of prohibited concomitant drugs within 7 days prior to screening 5) Subjects on hemodialysis, requiring hemodialysis at screening, with acute renal failure, or with a history of kidney transplant. 6) Previous administration of pregabalin ≥ 150 mg/day for subjects with moderate renal impairment (CrCL: 30-59 mL/min) or ≥ 75 mg/day for subjects with severe renal impairment (CrCL: 15-29 mL/min), declared lack of effect 7) Previous administration of gabapentin ≥ 600 mg/day for subjects with moderate renal impairment (CrCL: 30-59 mL/min) or ≥ 300 mg/day for subjects with severe renal impairment (CrCL: 15-29 mL/min), declared lack of effect 8) Malignancy other than basal cell carcinoma within the past 2 years prior to screening 9) Clinically significant unstable neurologic, ophthalmologic, hepatobiliary, respiratory, hematologic

	illness or unstable cardiovascular disease (eg, severe hypotension, uncontrolled cardiac arrhythmia, or myocardial infarction) within 12 months prior to screening 10) Clinically significant findings on electrocardiogram (ECG) at screening 11) History of pernicious anemia, untreated hypothyroidism, or human immunodeficiency virus infection 12) Known history of positive Hepatitis B antigen or Hepatitis C antibody 13) Pregnancy, potential pregnancy, breast feeding, or subjects unwilling to take reliable contraceptive measures during the study or for 4 weeks after study completion 14) Known hypersensitivity to pregabalin or gabapentin 15) Participation in another clinical study, either currently or within 30 days prior to providing of informed consent 16) Experience of participating in a DS-5565 clinical study and receiving investigational product 17) Abuse of illicit drugs or alcohol within 1 year prior to screening 18) Response of "yes" to any of the questions in the Columbia-Suicide Severity Rating Scale (C-SSRS) at screening or initiation of study treatment in relation to events occurring within the past 12 months 19) Previous treatment with drugs that could cause irreversible retinal degeneration 20) At screening, clinical laboratory values exceeding limits listed in Table 4-1 (see Section 4.1.3) 21) Subjects who are considered inappropriate for the study at the discretion of the investigator or sub-investigator For patients with DPNP only: 22) Hemoglobin A1c (National Glycohemoglobin Standardization Program) > 10.0% at screening

	23) Uncontrolled blood glucose at screening at initiation of study treatment that may require changes in diabetes treatment (non-insulin drug therapy, exercise therapy, diet therapy) during the study 24) Other severe pain at screening or initiation of study treatment, unrelated to diabetic peripheral neuropathy (DPN), that may confound the assessment of DPNP 25) Neurologic disorders at screening or initiation of study treatment, unrelated to DPN, that may confound the assessment of DPNP 26) Skin conditions that may confound the assessment of DPNP 27) Amputation of lower limb parts, other than toes, prior to screening or initiation of study treatment 28) Change of restricted concomitant drugs for patients with DPNP within 30 days prior to screening For patients with PHN only: 29) Previous use of neurolytic block (eg, chemical neurolytic block using phenol or ethyl alcohol, radiofrequency thermocoagulation) or neurosurgical therapy for current PHN 30) Other severe pain at screening or initiation of study treatment, unrelated to PHN, that may confound the assessment of PHN 31) Neurologic disorders at screening or initiation of study treatment, unrelated to PHN, that may confound the assessment of PHN 32) Skin conditions that may confound the assessment of PHN 33) Change of restricted concomitant drugs for patients with PHN within 14 days prior to screening 34) Use of prohibited concomitant therapies within 7 days prior to screening 35) Known immunocompromised status (eg, systemic lupus

	erythematosus, acquired immune deficiency syndrome, patients receiving immunosuppressants due to autoimmune disorder) For patients with DPNP and patients with PHN: 36) Response of "yes" to the suicidality question (current or past) on the Major Depressive Episode Module (Module A) or response of "yes" to any question of B1b, B3 through B11c, B13, or B14 in the Suicidality Module (Module B) on the Mini-international Neuropsychiatric Interview (MINI) (Version 6.0) Interview at screening
Dosage Form, Dose, and Route of Administration:	For subjects with moderate renal impairment at screening (CrCL: 30-59 mL/min): For the fixed dose period, DS-5565 at a total daily dose of 15 mg (7.5 mg BID), formulated in 2.5 mg and 5 mg tablets, will be administered orally twice daily (in the morning and at bedtime). For the titration period, DS-5565 will be administered with 5 mg (2.5 mg BID) during the first week, and followed by 10 mg (5 mg BID) during the second week. For subjects with severe renal impairment at screening (CrCL: 15-29 mL/min): For the fixed dose period, DS-5565 at a total daily dose of 7.5 mg (7.5 mg QD), formulated in 2.5 mg and 5 mg tablets, will be administered orally once daily (at bedtime). For the titration period, DS-5565 will be administered with 2.5 mg (2.5 mg QD) during the first week, and followed by 5 mg (5 mg QD) during the second week.
Study Endpoints:	Primary endpoint: The safety and tolerability of DS-5565 in subjects with moderate to severe renal impairment Secondary endpoints: • Change in ADPS from baseline to Week 14 • 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 including 15 pain descriptors (ranked on 4-stage intensity scale), the Present Pain Intensity index

	(ranked on a 6-stage intensity scale), and VAS (100-mm scale) • Patient Global Impression of Change assessed on a 7-point scale (from very much improved to very much worse) • Change from baseline in average daily sleep-interference score
Statistical Analyses:	For the safety endpoints, AEs, clinical laboratory test results, vital sign, ECG, physical findings (including body weight), C-SSRS, HADS, etc will be summarized by CrCL group using the safety analysis set. Quantitative data will be tabulated with descriptive summary statistics. For categorical data, frequency tables will be provided. All efficacy endpoints will be analyzed using the safety analysis set. Observed weekly ADPS and change from baseline will be summarized by CrCL group and week. Missing weekly ADPS values will be imputed based on a multiple imputation method using "nonfuture dependence" model which is specified by the pattern mixture approach with shifting parameters under missing not at random mechanism[11-13]. Each complete imputed dataset will be analyzed using the repeated measures analysis and Rubin's rule will be used to combine the results.

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LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ADPS	Average Daily Pain Score
ADR	Adverse Drug Reaction
ADSIS	Average Daily Sleep Interference Score
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
BID	*bis in die*
BUN	Blood Urea Nitrogen
Ca	Calcium
CMV	Cytomegalovirus
CNS	Central Nervous System
CrCL	Creatinine Clearance
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-Reactive Protein
C-SSRS	Columbia-Suicide Severity Rating Scale
DSMB	Data Safety Monitoring Board
DPN	Diabetic Peripheral Neuropathy
DPNP	Diabetic Peripheral Neuropathic Pain
EBV	Epstein-Barr Virus
ESRD	End Stage Renal Disease
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EDC	Electronic Data Capture
EIU	Exposure In Utero
ePRO	Electronic Patient Report Outcome
FDA	Food Drug Administration
FM	Fibromyalgia
FPI	First Patient In
GCP	Good Clinical Practice (refers to ICH and CFR)
γ-GT (γ-GTP)	gamma-Glutamyl Transpeptidase
GOT	Glutamic Oxaloacetic Transaminase
GPT	Glutamic Pyruvic Transaminase

ABBREVIATION	DEFINITION
HAC	Hepatic Adjudication Committee
HADS	Hospital Anxiety and Depression Scale
HbA1c	Hemoglobin A1c
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IgM	Immunoglobulin M
INN	International Nonproprietary Name
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LDH	Lactate Dehydrogenase
LOCF	Last Observation Carried Forward
LOE	Lack of Efficacy
LPLV	Last Patient Last Visit
LS	Least Squares
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MINI	Mini-international Neuropsychiatric Interview
MNAR	Missing Not At Random
NMDA	N-methyl-D-aspartate receptor
NRS	Numerical Rating Scale
PAP	PK Analysis Plan
PGIC	Patient Global Impression of Change
PHN	Post-Herpetic Neuralgia
PK	Pharmacokinetics
QD	*quaque die*
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SF-MPQ	Short-Form McGill Pain Questionnaire
TEAE	Treatment-Emergent Adverse Event
T-Bil	Total bilirubin
ULN	Upper Limit of Normal
US	United States
USA	United States of America
VAS	Visual Analog Scale
WBC	White Blood Cell

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1 Data Summary

1.1.1 Investigational Product(s)

1.1.1.1 Name

DS-5565

1.1.1.2 Description

DS-5565 binds with high affinity to the $\alpha_2\delta$ subunit of voltage-dependent Ca^{2+} channels. The $\alpha_2\delta$ subunit is expressed in the neural synapses, and analgesic action appears to be elicited when DS-5565 binds to this subunit.

1.1.1.3 Intended Use Under Investigation

Diabetic peripheral neuropathic pain (DPNP), post-herpetic neuralgia (PHN) or fibromyalgia (FM).

1.1.1.4 Nonclinical Studies

Evidence from nonclinical studies suggests that neuropathic pain 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 $\alpha_2\delta$ 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.[1,2,3,4]

In nonclinical experiments, DS-5565 showed potent and highly specific binding affinity to the $\alpha_2\delta$ subunit. DS-5565 also demonstrated a stronger analgesic effect than pregabalin in rodent models of neuropathic pain. Moreover, DS-5565 showed a renal-excreted type behavior in the results of ADME studies using rats and monkeys. Additional information on nonclinical studies can be found in the Investigator's Brochure.

1.1.1.5 Clinical Experience

Sixteen Phase 1 clinical pharmacology studies of DS-5565 and two Phase 2 studies of DS-5565 in patients with DPNP have been completed. Additionally, global Phase 3 studies are underway in patients with DPNP, PHN and FM.

1.1.1.5.1 [^{14}C]-labeled DS-5565 Mass Balance Study

In a [^{14}C]-labeled DS-5565 mass balance study (DS5565-A-U110) in healthy subjects given a single oral dose of 30 mg (N = 6), the mean total radioactivity recovered in urine and feces was 96.85% and 1.21% of the administered dose, respectively.

1.1.1.5.2 Pharmacological Studies in Subjects with Renal Impairment

Following administration of single oral doses of 5 mg DS-5565 to healthy subjects, subjects with mild, moderate, or severe renal impairment, and subjects with end stage renal disease (ESRD), the overall exposure to A200-0700, based on AUC, increased with severity of renal impairment (DS5565-A-E106 [N = 41] and DS5565-A-J115 [N = 30]). As assessed using the geometric least squares (LS) mean ratios, exposure was approximately 1-, 2-, 4-, and 5-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.

In a study in western subjects with varying degrees of renal function (DS5565-A-E106), a single 5 mg dose of DS-5565 was well tolerated. The majority of treatment-emergent adverse events (TEAEs) were considered by the investigator to be unrelated to study drug. Asthenia, fatigue, and somnolence were the only treatment-related TEAEs reported; these events occurred in the same subject.

In another study in Japanese subjects with varying degrees of renal function (DS5565-A-J115), a single 5 mg dose of DS-5565 was considered to be well tolerated in subjects with normal renal function or mild, moderate, or severe renal impairment. In subjects with ESRD, a single 5 mg dose of DS-5565 was also considered to be tolerated, but with a relatively high incidence of TEAEs. All TEAEs were mild or moderate, and not severe. The most common TEAEs (experienced by $\geq$ 2 subjects) were dizziness, somnolence, and vomiting, all of which occurred in subjects with ESRD.

1.1.1.5.3 Phase 2 Study in the US

This was a randomized, double-blind, placebo- and active-controlled study in subjects with DPNP in the US (N = 452).

In this study, greater mean decreases from baseline to end-of-treatment (Week 5) in average daily pain score (ADPS) were observed in the DS-5565 treatment groups than in the placebo group. The mean changes from baseline to Week 5 (with last observation carried forward (LOCF) imputed for missing values) in ADPS were -2.0, -2.3, -2.7, -2.6,

and -2.8 for the DS-5565 5 mg *quaque die* (QD), 10 mg QD, 15 mg QD, 10 mg *bis in die* (BID), and 15 mg BID treatment groups, respectively. By comparison, placebo and pregabalin showed mean changes of -1.9 and -1.8, respectively.

The primary analysis was an analysis of covariance (ANCOVA) on Week 5 LOCF data. The LS mean differences versus placebo in change in ADPS from baseline to Week 5 were -0.22, -0.53, -0.94, -0.88, and -1.01 for the DS-5565 5 mg QD, 10 mg QD, 15 mg QD, 10 mg BID, and 15 mg BID treatment groups, respectively. These LS mean differences were statistically significant at the DS-5565 15 mg QD ($P = 0.0137$), 10 mg BID ($P = 0.0171$), and 15 mg BID ($P = 0.0060$) dose levels.

In this study, all DS-5565 dose levels were generally well tolerated.

At least 1 TEAE was reported in 52.7% of subjects receiving DS-5565 5 mg QD, 50.0% of subjects receiving DS-5565 10 mg QD, 56.6% of subjects receiving DS-5565 15 mg QD, 58.9% of subjects receiving DS-5565 10 mg BID, 63.2% of subjects receiving DS-5565 15 mg BID, 44.4% of subjects receiving placebo, and 60.0% of subjects receiving pregabalin. Common TEAEs (ie, those reported in ≥ 5% of subjects receiving DS-5565) were dizziness (9.4%), headache (6.1%), and somnolence (6.1%). Most TEAEs were mild or moderate in severity, and all severe TEAEs resolved except for 1 event each of hepatic cirrhosis and osteoarthritis. At least 1 TEAE of special interest (eg, central nervous system [CNS]-related events, edema, visual disorders, hepatic-related events, cardiac-related events, events related to abuse potential) was reported in 10.9% of subjects receiving DS-5565 5 mg QD, 19.6% of subjects receiving DS-5565 10 mg QD, 26.4% of subjects receiving DS-5565 15 mg QD, 19.6% of subjects receiving DS-5565 10 mg BID, 28.1% of subjects receiving DS-5565 15 mg BID, 7.4% of subjects receiving placebo, and 28.0% of subjects receiving pregabalin.

In this study, a 73-year old white male in the DS-5565 15 mg QD group experienced severe liver function test abnormal. The subject completed the 5-week study drug treatment period. One day after the last dose of study medication, asymptomaticincreases of alanine aminotransferase (ALT) (18.54 × Upper Limit of Normal [ULN]), aspartate aminotransferase (AST) (14.17 × ULN), and total bilirubin (2.75 × ULN)(concomitant non-serious TEAE of blood bilirubin increased) were observed, as well as alkaline phosphatase (ALP) value of 1.02 × ULN. The subject denied alcohol intake, had not traveled recently, and had no prior history of elevated transaminases. The subject returned to the site for clinical evaluation at multiple follow

up visits without signs or symptoms. Follow-up hepatitis panel results included negative hepatitis B core Total, hepatitis C virus, and hepatitis A virus immunoglobulin M (IgM); negative Epstein-Barr virus IgM (EBV IgM); positive EBV IgG; and negative antinuclear antibody. Follow-up abdominal ultrasound revealed an echogenic liver that was considered possibly due to fatty infiltration, a 1.5 cm gallstone without biliary dilatation, no gallbladder wall thickening, and an 8 cm simple left renal cyst. The subject recovered from the events of blood bilirubin increased and liver function test abnormal 14 days later. The patient remained asymptomatic throughout the course of events. Workup included, hepatitis serologies including hepatitis A, B, and C, which were all negative. Epstein-Barr virus antibodies were suggestive of a past infection. Hepatic ultrasound, performed 6 days after the abnormal laboratory findings, demonstrated findings suggestive of fatty infiltration and a 1.5-cm gallstone without evidence of biliary distension. The event of blood bilirubin increased and the serious adverse event of liver function test abnormal were both considered by the investigator as resolved and related to the study drug.

1.1.1.5.4 Phase 2 Study in Asia

This was a randomized, double-blind, placebo- and active-controlled study in subjects with DPNP in Asia (N = 450).

The primary endpoint was the change in ADPS from baseline to Week 7 (with LOCF imputed for missing values). For the primary analysis, an ANCOVA was performed using treatment as the factor and baseline ADPS as the covariate to compare the mean change from baseline to Week 7/LOCF between each DS-5565 treatment group and placebo, between each DS-5565 treatment group and pregabalin, and between pregabalin and placebo. The mean changes from baseline to Week 7/LOCF in ADPS were -1.8, -1.8, and -1.7 for DS-5565 5 mg BID, 10 mg BID, and 15 mg BID treatment groups. By comparison, placebo and pregabalin showed mean changes of -1.5 and -1.5, respectively. The primary analysis was an ANCOVA on Week 7 LOCF data. The LS mean differences versus placebo in change in ADPS from baseline to Week 7/LOCF were -0.42, -0.37, and -0.30 for the DS-5565 5 mg BID, 10 mg BID, and 15 mg BID treatment groups, respectively. These LS mean differences were numerically lower than that in the placebo group, although the reduction was not statistically significant for any treatment groups.

All DS-5565 dose levels were generally well tolerated. Based on dose level, at least 1 TEAE was experienced by 48.9% of subjects in the DS-5565 5 mg BID group, 63.4% of

subjects in the DS-5565 10 mg BID group, 73.3% of subjects in the DS-5565 15 mg BID group, 58.1% of subjects receiving pregabalin 150 mg BID, and 53.4% of subjects receiving placebo. Common TEAEs (ie, those reported in ≥ 5% of subjects receiving DS-5565) were: somnolence (14.7%), dizziness (11.0%), nasopharyngitis (8.4%).

Two deaths due to completed suicide were reported in subjects receiving 5 mg BID and 10 mg BID of DS-5565; these deaths occurred in Japan. One subject receiving 10 mg DS-5565 BID completed suicide 36 days after the first dose of study drug and 1 day after the most recent dose. The second subject receiving 5 mg DS-5565 BID completed suicide 18 days after study treatment had ended (non-treatment-emergent by protocol definition).

In both cases, the investigators considered the suicide events to be unrelated to the study drug. For the one subject receiving 10 mg BID, suicide risk had been assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS) at pretreatment, with no findings of suicidal tendency. The subject's anxiety and depression scores, as assessed by the Hospital Anxiety and Depression Scale (HADS), did not identify specific problems. For the second subject receiving 5 mg BID, the C-SSRS was administered pretreatment and at Visit 6; neither testing demonstrated an indication of suicidal tendency. The subject's anxiety and depression scores, as assessed by the HADS, did not identify specific problems from pretreatment to end-of-treatment. No physical or psychological abnormality had been noted at the last visit.

1.2 Study Rationale

Currently available $\alpha_2\delta$ ligands, gabapentin and pregabalin, are established as effective first-line treatments for pain associated with diabetic peripheral neuropathy (DPN) [3] and PHN[5]. However, the dosage, and thus efficacy, of these agents is limited by frequent and significant CNS-related side effects, including dizziness and somnolence; associated weight gain and peripheral edema can also be problematic. As a result, a large proportion of patients with DPNP and PHN are left with insufficient pain relief, and new treatment options are needed.

DS-5565 is an oral analgesic drug being developed for DPNP, PHN and other indications. This study is being conducted in patients with renal impairment, because DPNP and PHN are common in the elderly and the renal function is often impaired in elderly patients.

Therefore, DS-5565 is assumed to be used for treatment of the patients with renal impairment widely. Renal excretion is the main clearance pathway of DS-5565, therefore the exposure of DS-5565 depends on the renal function. The present study aims to evaluate the safety of DS-5565 for treating pain in subjects with DPNP with renal impairment and PHN with renal impairment.

1.3 Risks and Benefits for Study Subjects

The clinical efficacy of DS-5565 has been established in 2 Phase 2, multi-center, randomized, double-blind, placebo-, and active-comparator controlled adaptive studies in subjects with DPNP. In DS5565-A-U201 conducted in the US, DS-5565 15 mg QD, 10 mg BID, and 15 mg BID treatment groups demonstrated statistically significant mean reductions in ADPS from baseline to end-of-treatment compared to placebo. In DS5565-A-J202 conducted in Asian countries, DS-5565, 5, 10, and 15 mg BID showed numerically mean reductions in ADPS, although the reductions were not statistically significant. The results were supportive of the US study. These data provide proof-of-concept for DS-5565 as a treatment for DPNP and suggest that DS-5565 may have utility in other chronic pain conditions, such as PHN and FM.

Anticipated risks of DS-5565 include the occurrence of adverse reactions related to CNS depression, such as dizziness and somnolence, as well as peripheral edema. Other notable TEAEs that have been observed in Phase 1 and Phase 2 studies include elevations of hepatic transaminases and suicide/suicidal ideation, both of which are carefully monitored and assessed as AESI in the ongoing Phase 3 DPNP, PHN, and FM programs. Ongoing monitoring of the Phase 3 program has identified no new safety concerns. For the approved $\alpha_2\delta$ 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. Given the totality of clinical and nonclinical data, the current risk management approach appropriately safeguards subject safety, and the risk/benefit assessment is deemed positive.

In patients with moderate to severe renal impairment, sufficient efficacy of DS-5565 and acceptable risk of TEAEs on CNS are expected by the administration of the drug at an appropriate dosage based on the estimated exposure to the drug in those patients.

2. STUDY OBJECTIVES AND HYPOTHESES

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective is to characterise the safety and tolerability of DS-5565 in subjects with moderate to severe renal impairment.

2.1.2 Secondary Objectives

- To evaluate the effect of DS-5565 on the ADPS
- To evaluate the ADPS responder rate (the proportion of subjects with ≥ 30% and ≥ 50% reduction from baseline to Week 14)
- To evaluate the effect of DS-5565 on additional pain questionnaire, using the Short-Form McGill Pain Questionnaire ([SF-MPQ]: sensory, affective, and total subscales, Visual Analog Scale [VAS], and present pain intensity).
- To assess the effect of DS-5565 on sleep and patient impressions in pain.
- To evaluate pharmacokinetic of DS-5565.

2.2 Study Hypothesis

The primary hypothesis of this open-label study is that DS-5565 will be generally safe and well-tolerated when the drug is administered with a dosing of 7.5 mg BID in subjects with moderate renal impairment (Creatinine Clearance [CrCL]: 30-59 mL/min) and 7.5 mg QD in subjects with severe renal impairment (CrCL: 15-29 mL/min).

3. STUDY DESIGN

3.1 Overall Plan

3.1.1 Study Type

This is an open-label study for treatment of DPNP or PHN in subjects with moderate to severe renal impairment.

Study sites: Approximately 35 study sites in Japan.

Planned sample size: Approximately 35 subjects will be enrolled in the study.

3.1.2 Study Scheme

The total study duration (for an individual subject's participation) is approximately 16 weeks, consisting of an observation period (1 week), a titration period (2 weeks), a fixed dose period (12 weeks), and a follow-up period (1 week) (See study scheme below).

For subjects with DPNP:

If prohibited concomitant medications are used within 7 days prior to obtaining written informed consent, screening will follow a washout period of at least 7 days. Informed consent must be obtained before initiating washout or screening. Enrollment will be limited to subjects who meet the inclusion/exclusion criteria described in Section 4.1.2 and Section 4.1.3.

For subjects with PHN:

If prohibited concomitant medications or prohibited concomitant therapies are used within 7 days prior to obtaining written informed consent, screening will follow a washout period of at least 7 days. Informed consent must be obtained before initiating washout or screening. Enrollment will be limited to subjects who meet the inclusion/exclusion criteria described in Section 4.1.2 and Section 4.1.3.

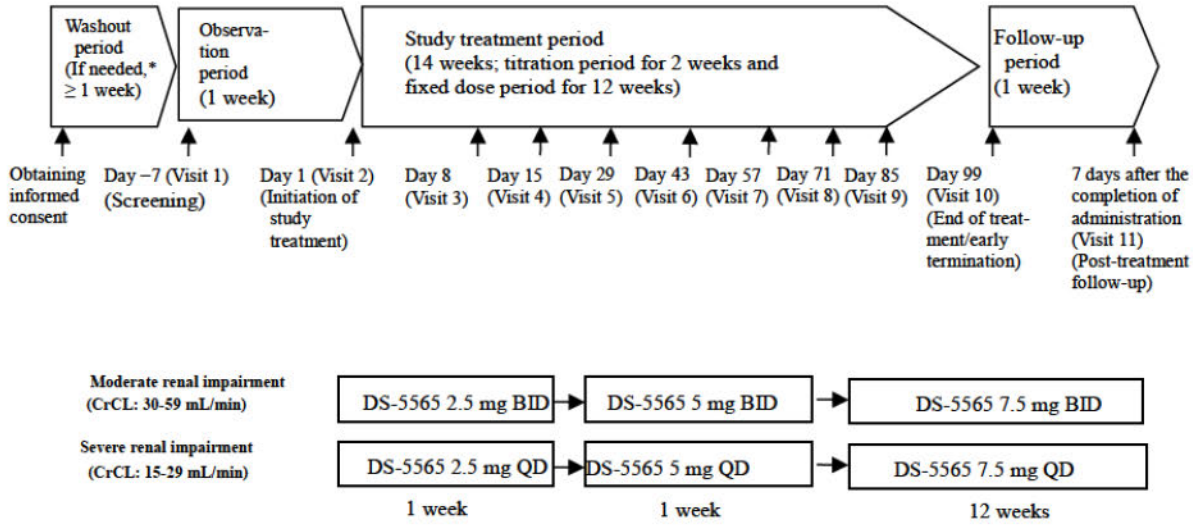
For subjects with moderate renal impairment (CrCL: 30-59 mL/min):

After the observation period, the first week will be the titration period with administration of 2.5 mg BID. For the second week, the investigational product is administrated at dose of 5 mg BID. For the fixed dose period, the investigational product is administrated at dose of 7.5 mg BID. After the completion of administration, subjects will be monitored for an additional follow-up period of 1 week.

For subjects with severe renal impairment (CrCL: 15-29 mL/min):

After the observation period, the first week will be the titration period with administration of 2.5 mg QD. For the second week, the investigational product is administrated at dose of 5 mg QD. For the fixed dose period, the investigational product is administrated at dose of 7.5 mg QD. After the completion of administration, subjects will be monitored for an additional follow-up period of 1 week.

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



* For subjects with DPNP:
After informed consent is obtained, subjects who are under treatment with prohibited concomitant medications (see Section 5.2.1 will undergo a washout period of 7 days or more.
For subjects with PHN:
After informed consent is obtained, subjects who are under treatment with prohibited concomitant medications or prohibited concomitant therapies (see Section 5.2.1 and Section 5.2.4) will undergo a washout period of 7 days or more.

3.1.3 Study Endpoints

3.1.3.1 Primary Endpoint

The safety and tolerability of DS-5565 in subjects with moderate to severe renal impairment

3.1.3.2 Secondary Endpoints

- Change in ADPS from baseline to Week 14
- 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 including 15 pain descriptors (ranked on a 4-stage intensity scale), the Present Pain Intensity index (ranked on a 6-stage intensity scale), and VAS (100-mm scale)
- Patient Global Impression of Change (PGIC) assessed on a 7-point scale (from very much improved to very much worse)
- Change from baseline in average daily sleep-interference score (ADSIS)

3.1.4 Duration of Subject Participation

The duration of subject participation will be approximately 16 weeks, including an observation period, a titration period, a fixed dose period, and a follow-up period.

3.2 Discussion of Study Design

3.2.1 Dosage of DS-5565

Dose regimens were selected based on results of single-dose studies in subjects with renal impairment volunteers, as well as modeling and simulation. Study DS5565-A-J115 was conducted to assess pharmacokinetics (PK) of DS-5565 in Japanese subjects with renal impairment. As the result of DS5565-A-J115, no notable differences were found in C_{max} among the subjects with normal, mild, and moderate renal impairment. However, the C_{max} was higher in the subjects with severe renal impairment. The geometric LS mean ratio of C_{max} in comparison to the subjects with normal renal function was 1.5 for the subjects with severe renal impairment. The AUC_{last} increased with severity of renal impairment: the AUC_{last} was 1.3 times higher for the subjects with mild renal impairment, 1.9 times higher for moderate renal impairment, 3.6 times higher for severe renal impairment. These results were similar to the results of Study DS5565-A-E106, which was conducted to assess PK of DS-5565 in Western subjects with renal impairment. Population PK analysis was conducted for Study DS5565-A-E106 to evaluate the effect of CrCL on DS-5565 exposure. The treatment groups were analyzed by normal CrCL (≥ 90 mL/min), mild reduction in CrCL (60 to 89 mL/min), moderate reduction in CrCL (30 to 59 mL/min), and severe reduction in CrCL (15 to 29 mL/min). Relative to subjects with normal renal function, total clearance of

DS-5565 was predicted about 11%, 56%, and 73% lower than in subjects with mild, moderate, and severe renal impairment, respectively. Based on these results, a half dose in subjects with moderate renal impairment and a quarter dose in subjects with severe renal impairment are expected to be equivalent exposure to a dose in subjects with normal renal function. A BID doses of 15 mg was selected as a maximum dosing regimen in Phase 3 studies (DS5565-A-J303, DS5565-A-J304), therefore BID doses of 7.5 mg and QD doses of 7.5 mg in subjects with moderate and severe renal dysfunction, respectively are expected to produce exposures equivalent to a BID doses of 15 mg in subjects with normal renal function (Table 3-1).

Along with on-going Phase 3 studies (DS5565-A-J303, DS5565-A-J304), the duration of the titration period of this study is 2 weeks.

Table 3-1Predicted DS-5565 AUC and C_{max} with Once Daily and Twice Daily Doses of 7.5-15 mg in Subjects with Renal Dysfunction (Estimation from DS5565-A-E106)

CrCL Group (mL/min)	**Dose**	**$AUC_{ss,0-24h}$ (ng*h/mL)**		**$C_{max,ss}$ (ng/mL)**	
		Mean	**Median (min, max)**	**Mean**	**Median (min, max)**
≥ 90	15 mg BID	1720	1616 (1311, 2806)	226	233 (176, 281)
60-89	15 mg BID	1899	1823 (1536, 2281)	239	226 (162, 327)
30-59	7.5 mg BID	1741	1850 (1345, 2080)	163	161 (119, 209)
15-29	7.5 mg QD	1529	1488 (1260, 1958)	152	156 (118, 177)

AUC = area under the plasma concentration-time curve; $AUC_{ss,0-24h}$ = area under the plasma concentration-time curve at steady state from 0 to 24 hours; $C_{max,ss}$ = maximum plasma concentration at steady state; CrCL = creatinine clearance; BID = twice daily; QD = once daily

3.2.2 Duration of Study Treatment

The duration of study treatment is the same as the Asian phase 3 studies (DS5565-A-J303, and DS5565-A-J304). These studies evaluate the efficacy of DS-5565 in patients with DPNP or PHN in a double-blind manner. In these double-blind studies, the efficacy of DS-5565 versus placebo in neuropathic pain will be evaluated. The European

Medicines Agency guideline[6] recommends that the treatment duration for fixed dose period should be 12 weeks or longer. Therefore, the study will have 12 weeks of fixed dose period. In addition, taking into consideration for subject safety, the study will have 2 weeks of titration period before the fixed dose period.

3.2.3 Study Endpoints

The safety endpoints were selected to evaluate the safety of DS-5565 in subjects with renal impairment. AEs, clinical laboratory evaluations, ECG, and vital sign are commonly evaluated for safety assessment in clinical studies. Body weight was selected to evaluate edema, which is a known adverse reaction of DS-5565.

Assessments by HADS and C-SSRS were selected to evaluate the risk of anxiety, depression, or suicidal tendency. Neurological examination was selected to evaluate gait/station and muscle strength. The efficacy endpoints were selected to evaluate the effect of DS-5565 on pain reduction, sleep interference, and the symptoms of DPNP or PHN.

4. STUDY POPULATION

4.1 Enrollment

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

4.1.1 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 IWRS at screening. For subjects with DPNP, any subjects who have been taking prohibited concomitant drugs will undergo a washout period of 7 days or more, prior to the screening. For subjects with PHN, any subjects who have been taking prohibited concomitant drugs or receiving prohibited concomitant therapy will undergo a washout period of 7 days or more, prior to the screening. After the screening visit (Visit 1), a 7-day observation period will be implemented before initiation of study treatment.

At initiation of study treatment (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.

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

4.1.2 Inclusion Criteria

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

For patients with DPNP and patients with PHN:

1) Age ≥ 20 years at informed consent
2) Able to give written informed consent for study participation, understand procedures of this study, and complete patient-reported questionnaires adequately
3) CrCL (using the Cockcroft-Gault equation): 15-59 mL/min at screening
4) At screening, a pain scale of ≥ 40 mm on VAS of SF-MPQ
5) At initiation of study treatment, 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)

For patients with DPNP only:

6) Type 1 or type 2 diabetes mellitus at screening
7) Painful distal symmetric polyneuropathy, diagnosed at least 6 months prior to screening (see Procedures manual for the Diagnosis of Diabetic Peripheral Neuropathy and Neurological Examination for details)

For patients with PHN only:

8) PHN defined as pain present for 3 months or more after herpes zoster skin rash at screening

Rationale

1) Phase 1 and Phase 2 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 PK and 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) The study will investigate in subjects with severe to moderate renal impairment.
4), 5) 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.
6), 7) The study will investigate DPNP.
8) The study will investigate PHN.

4.1.3 Exclusion Criteria

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

For patients with DPNP and patients with PHN:

1) At screening, a pain scale of ≥ 90 mm on VAS of SF-MPQ
2) At initiation of study treatment, a pain scale of ≥ 90 mm on VAS of SF-MPQ, or at least a daily pain score of ≥ 9 during observation period
3) Major psychiatric disorders at screening or initiation of study treatment
4) Use of prohibited concomitant drugs within 7 days prior to screening

5) Subjects on hemodialysis, requiring hemodialysis at screening, with acute renal failure, or with a history of kidney transplant.
6) Previous administration of pregabalin ≥ 150 mg/day for subjects with moderate renal impairment (CrCL: 30-59 mL/min) or ≥ 75 mg/day for subjects with severe renal impairment (CrCL: 15-29 mL/min), declared lack of effect
7) Previous administration of gabapentin ≥ 600 mg/day for subjects with moderate renal impairment (CrCL: 30-59 mL/min) or ≥ 300 mg/day for subjects with severe renal impairment (CrCL: 15-29 mL/min), declared lack of effect
8) Malignancy other than basal cell carcinoma within the past 2 years prior to screening
9) Clinically significant unstable neurologic, ophthalmologic, hepatobiliary, respiratory, hematologic illness or unstable cardiovascular disease (eg, severe hypotension, uncontrolled cardiac arrhythmia, or myocardial infarction) within 12 months prior to screening
10) Clinically significant findings on ECG at screening
11) History of pernicious anemia, untreated hypothyroidism, or human immunodeficiency virus infection
12) Known history of positive Hepatitis B antigen or Hepatitis C antibody
13) Pregnancy, potential pregnancy, breast feeding, or subjects unwilling to take reliable contraceptive measures during the study or for 4 weeks after study completion
14) Known hypersensitivity to pregabalin or gabapentin
15) Participation in another clinical study, either currently or within 30 days prior to providing of informed consent
16) Experience of participating in a DS-5565 clinical study and receiving investigational product
17) Abuse of illicit drugs or alcohol within 1 year prior to screening
18) Response of "yes" to any of the questions in the C-SSRS at screening or initiation of study treatment in relation to events occurring within the past 12 months
19) Previous treatment with drugs that could cause irreversible retinal degeneration
20) At screening, clinical laboratory values exceeding limits listed in Table 4-1
21) Subjects who are considered inappropriate for the study at the discretion of the investigator or sub-investigator

For patients with DPNP only:

22) Hemoglobin A1c (HbA1c) (National Glycohemoglobin Standardization Program) > 10.0% at screening
23) Uncontrolled blood glucose at screening or initiation of study treatment that may

require changes in diabetes treatment (non-insulin drug therapy, exercise therapy, diet therapy) during the study

24) Other severe pain at screening or initiation of study treatment, unrelated to DPN, that may confound the assessment of DPNP
25) Neurologic disorders at screening or initiation of study treatment, unrelated to DPN, that may confound the assessment of DPNP
26) Skin conditions that may confound the assessment of DPNP
27) Amputation of lower limb parts, other than toes, prior to screening or initiation of study treatment
28) Change of restricted concomitant drugs for patients with DPNP within 30 days prior to screening

For patients with PHN only:

29) Previous use of neurolytic block (eg, chemical neurolytic block using phenol or ethyl alcohol, radiofrequency thermocoagulation) or neurosurgical therapy for current PHN
30) Other severe pain at screening or initiation of study treatment, unrelated to PHN, that may confound the assessment of PHN
31) Neurologic disorders at screening or initiation of study treatment, unrelated to PHN, that may confound the assessment of PHN
32) Skin conditions that may confound the assessment of PHN
33) Change of restricted concomitant drugs for patients with PHN within 14 days prior to screening
34) Use of prohibited concomitant therapies within 7 days prior to screening
35) Known immunocompromised status (eg, systemic lupus erythematosus, acquired immune deficiency syndrome, patients receiving immunosuppressants due to autoimmune disorder)

For patients with DPNP and patients with PHN:

36) Response of "yes" to the suicidality question (current or past) on the Major Depressive Episode Module (Module A) or response of "yes" to any question of B1b, B3 through B11c, B13, or B14 in the Suicidality Module (Module B) on the Mini-international Neuropsychiatric Interview (MINI) (Version 6.0) Interview at screening

Table 4-1 Hematology/Blood Chemistry Limits

Hematology	Hemoglobin	< 8 g/dL
	Platelet Count	< 100 000/mm^3
	Absolute Neutrophil Count	< 1500/mm^3
Blood Chemistry	AST (GOT)	> 2.0 × ULN
	ALT (GPT)	> 2.0 × ULN
	ALP	> 1.5 × ULN
	T-Bil	> 1.2[a] × ULN
	Creatine Kinase	> 3.0 × ULN

a: If a subject has total bilirubin 1.2 > ULN: unconjugated and conjugated bilirubin fractions should be analyzed and only subjects documented to have Gilbert's syndrome may be enrolled.

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, GOT = glutamic oxaloacetic transaminase, GPT = glutamic pyruvic transaminase, T-Bill = total bilirubin, ULN = upper limit of normal

Rationale

1), 2) These criteria were 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.

3), 4), 5), 22), 23), 24), 25), 26), 27), 28), 29), 30), 31), 32), 33), 34) These criteria were selected so that efficacy and safety could be appropriately assessed in subjects.

6), 7), 16) These criteria were selected out of consideration for efficacy assessment in subjects.

8), 9), 10), 11), 12), 13), 14), 15), 17), 18), 19), 20), 21), 35), 36) These criteria were selected out of consideration for the safety of subjects.

4.2 Subject Withdrawal

Data from all medicated subjects are important to achieve study objectives, and subjects should be encouraged to adhere to protocol instructions and visit schedules. However, in accordance with the Declaration of Helsinki and other applicable regulations, a subject has the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the study physician or at the study site. The

investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants such action. The sponsor or regulatory authorities also may request termination of the study at any time due to safety issues or concerns related to study conduct.

4.2.1 Withdrawal Criteria

If a subject meets the following withdrawal criteria, that subject should be withdrawn from the study.

- Difficulty of continuing the study due to AE
- Subjects with any of the following elevations in clinical laboratory values
  - 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 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)
- Decrease in CrCL < 15 mL/min
- AE related to suicide (if there are any "yes" responses to any of the questions in the C-SSRS)
- Withdrawal by subject (ie, withdrawal of consent)
- Major deviation from study procedure

4.2.2 Reasons for Withdrawal

If a subject discontinues from the study treatment for any reason, the date and the reason for discontinuation must be recorded in the Electronic Case Report Form (eCRF) using the following criteria.

For subjects withdrawn prior to randomization but after signing informed consent

- Screen failure
- Withdrawal by subject (eg, AE, Lack of efficacy [LOE], Other)
- Physician decision
- Other

For subjects withdrawn after the initiation of study treatment but before completing the study as per protocol

- AE
- Death
- LOE
- Lost to follow-up
- Protocol violation
- Decrease in CrCL < 15 mL/min
- 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 4.2.3 and Section 6.4).

4.2.3 Withdrawal Procedures

If a 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/Early Termination Visit (Visit 10) will be conducted, assessments will be made at that time point, all observations and tests scheduled for the Post-treatment Follow-up Visit (Visit 11) 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 1 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 Case Report Form (CRF) (see Section 9.1.4). 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.

4.2.4 Stopping Rules for the Study

Circumstances under which the study may be stopped based upon independent Data Safety Monitoring Board (DSMB) recommendation are specified in Section 11.9. Specific stopping criteria have been set up regarding 2 potential safety concerns (hepatic events and suicide) as follows:

Hepatic events study stopping rules:

If there is one adjudicated Hy's law case (concurrent increases in ALT or AST $\geq 3 \times$ ULN, T-Bil $\geq 2 \times$ ULN, and causally relaeted) on DS-5565 in any of the Phase 3 studies and/or the entire Phase 3 program.

Suicide study stopping rules:

If 4 or more completed suicides are assessed by the DSMB to be related to DS-5565 (with an imbalance of 2 more cases versus placebo) in any of the Phase 3 studies and/or the entire Phase 3 program.

In addition, the study may be terminated at any time at the sponsor's discretion.

5. TREATMENT ADMINISTERED

5.1 Investigational Products

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

5.1.1 Study Treatments

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

5.1.1.1 Investigational Product

Investigational product code: DS-5565

Chemical name: [(*1R,5S,6S*)-6-(aminomethyl)-3-ethylbicyclo[3.2.0]hept-3-en-6-yl] acetic acid monobenzenesulfonate

Content and dosage form:

Name of investigational product	Content and dosage form
DS-5565 Tablet 2.5 mg	White film-coated tablet containing 2.5 mg of the free form of DS-5565
DS-5565 Tablet 5 mg	White film-coated tablet containing 5 mg of the free form of DS-5565

5.1.2 Dosing Regimens for the Study

The duration of investigational product administration will be 14 weeks, consisting of a titration period and a fixed dose period. As Table 5-1 shows, the treatment period will begin at bedtime on Day 1 (Visit 2) and will continue until the morning of Day 99 (Visit 10).

5.1.2.1 Dosing Regimens for the Subject with Moderate Renal Impairment

During the treatment period, 1 tablet (for titration period) or 2 tablets (for fixed dose period) DS-5565 will be administered orally twice daily (in the morning and at bedtime). The subject must select the administration timing, either fasted or fed in the morning at initiation of study treatment (Visit 2), and it will be followed during the treatment period.

5.1.2.2 Dosing Regimens for the Subject with Severe Renal Impairment

During the treatment period, 1 tablet (for titration period) or 2 tablets (for fixed dose period) DS-5565 will be administered orally once daily at bedtime.

Table 5-1: Method of Administration During the Treatment Period

	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
Moderate renal impairment (CrCL: 30-59 mL/min)	—	2.5	2.5	2.5	2.5	5	5	5	5	7.5	7.5	7.5	7.5	—
Severe renal impairment (CrCL: 15-29 mL/min)	—	2.5	—	2.5	—	5	—	5	—	7.5	—	7.5	—	—

5.1.3 Method of Assessing Treatment Compliance

All subjects in this study will commence therapy as outpatients, and the investigational product will be self-administered orally. Subjects will take 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 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.

5.1.4 Labeling and Packaging

DS-5565 tablets of 2.5 mg and 5 mg will be packaged separately in aluminium blister packs. Packages for the treatment period will be prepared for the combinations shown in Table 5-2 and Table 5-3. Three types of box for DS-5565 tablets of 2.5 mg, 5 mg and administration for 7.5 mg which is packed in 2.5 mg tablet and 5 mg tablet will contain the investigational product for the treatment period. 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, and the name and address of the sponsor 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 5-2: Drug Combinations During the Treatment Period for Subjects with Moderate Renal impairment (CrCL: 30-59 mL/min)

Treatment period	Investigational product combination	
	Morning	Bedtime
Week 1	(2.5)	(2.5)
Week 2	(5)	(5)
Week 3 to Week 14	(2.5) (5)	(2.5) (5)

(2.5) DS-5565 tablet 2.5 mg

(5) DS-5565 tablet 5 mg

Table 5-3: Drug Combinations During the Treatment Period for Subjects with Severe Renal impairment (CrCL: 15-29 mL/min)

Treatment period	Investigational product combination	
	Morning	Bedtime
Week 1	—	(2.5)
Week 2	—	(5)
Week 3 to Week 14	—	(2.5) (5)

(2.5) DS-5565 tablet 2.5 mg

(5) DS-5565 tablet 5 mg

5.1.5 Storage

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

5.1.6 Drug Accountability

The sponsor will deliver the investigational product as needed to the investigational product administrator designated at the study site. The administrator will store and manage the investigational product based on the manual for management of investigational product, and will maintain records and prepare reports as required.

5.2 Concomitant Medications and Treatments

Any concomitant medications except rescue medications (see Section 5.2.3) and any concomitant treatments conducted to a subject during the period from the time of obtaining informed consent until Visit 11, whether permitted or not, will be documented in the 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.

5.2.1 Prohibited Concomitant Medications

5.2.1.1 Prohibited Concomitant Medication for Patients with DPNP

The following drugs are prohibited for concomitant use from the screening (Visit 1) through the post-treatment follow-up (Visit 11). The patients given drugs that could cause irreversible retinal degeneration must be excluded. After informed consent is obtained, subjects who are under treatment with the following prohibited concomitant drugs will undergo a washout period of 7 days or more. Visit 1 will occur after completion of this washout period.

1) Pregabalin
2) Antiepileptics (gabapentin, carbamazepine, etc.)
3) Antidepressants (other than selective serotonin reuptake inhibitors)
4) Hypnotics, anxiolytics (other than ultrashort acting drugs [triazolam, zopiclone, zolpidem tartrate])
5) Opioids
6) Tramadol
7) Neurotropin®
8) *N*-methyl-*D*-aspartate receptor (NMDA) antagonists (dextromethorphan, ketamine, memantine, etc.)
9) Non-steroidal anti-inflammatory drugs (except topical product for other than disease site of DPN)
10) Muscle relaxants
11) Topical capsaicin (except topical product for other than disease site of DPN)
12) Local anesthetics (lidocaine, etc.) (except topical product for other than disease site of DPN)
13) Na channel blockers (mexiletine, etc.)
14) Centrally acting sympatholytic agents (clonidine, etc.)
15) Steroids (except topical product for other than disease site of DPN)
16) Cilostazol, prostaglandin (except topical product for other than disease site of DPN)

17) Chinese herbal medicines with analgesic effects on neuropathic pain (life-preserving kidney-qi pill, peony and licorice decoction, eight-ingredient pill with rehmannia, etc.)
18) Vitamins B1 and B12 (except topical product for other than disease site of DPN)
19) α-lipoic acid
20) γ-linolenic acid (evening primrose oil)
21) Aldose reductase inhibitors
22) Drugs that could cause irreversible retinal degeneration (phenothiazine antipsychotics, deferoxamine, quinine, quinidine, ethambutol, voriconazole, etc.)
23) Other investigational products

5.2.1.2 Prohibited Concomitant Medications for Patients with PHN

The following drugs are prohibited for concomitant use from the screening (Visit 1) through the post-treatment follow-up (Visit 11). The patients given drugs that could cause irreversible retinal degeneration must be excluded. After informed consent is obtained, subjects who are under treatment with the following prohibited concomitant drugs will undergo a washout period of 7 days or more. Visit 1 will occur after completion of this washout period.

1) Pregabalin
2) Antiepileptics (gabapentin, carbamazepine, etc.)
3) Hypnotics, anxiolytics (other than ultrashort acting drugs [triazolam, zopiclone, zolpidem tartrate])
4) Opioids
5) Tramadol (including its combination drug)
6) Neurotropin®
7) NMDA antagonists (dextromethorphan, ketamine, memantine, etc.)
8) Muscle relaxants
9) Topical capsaicin(except topical product for other than disease site of PHN)
10) Local anesthetics (lidocaine, etc.) (except topical product for other than disease site of PHN)
11) Na channel blockers (mexiletine, etc.)
12) Centrally acting sympatholytic agents (clonidine, etc.)
13) Steroids (except topical product for other than disease site of PHN)
14) Prostaglandin and related products (except topical product for other than disease site of PHN)
15) Vitamins B1 and B12 (prescribed for PHN)

16) α-lipoic acid
17) γ-linolenic acid (evening primrose oil)
18) Nefopam
19) Immunosuppressants (prescribed for autoimmune disorder)
20) Drugs that could cause irreversible retinal degeneration (phenothiazine antipsychotics, deferoxamine, quinine, quinidine, ethambutol, voriconazole, etc.)
21) Other investigational products

5.2.2 Restricted Concomitant Medications

5.2.2.1 Restricted Concomitant Medications for Patients with DPNP

The following drugs are permitted for concomitant use if their dosage has not changed for 30 days prior to Visit 1. These drugs may be used concomitantly from the screening (Visit 1) through the post-treatment follow-up (Visit 11), but the dosage may not be changed.

1) Antidiabetic drugs other than insulin
2) Selective serotonin reuptake inhibitors (SSRI) (limited to the treatment of depression and anxiety)
3) Hypnotics (only ultrashort acting drugs [triazolam, zopiclone, zolpidem tartrate])
4) Ameliorator for peripheral circulation (except for cilostazol and prostaglandin)
5) Aspirin (only for preventing thrombosis and embolism [eg, myocardial infarction and stroke], should be used according to the package insert)

5.2.2.2 Restricted Concomitant Medications for Patients with PHN

The following drugs are permitted for concomitant use if their dosage has not changed for 14 days prior to Visit 1. These drugs may be used concomitantly from the screening (Visit 1) through post-treatment follow-up (Visit 11), but the dosage may not be changed and these drugs are not allowed to stop (Only if safety problem has observed by using these drugs, dose reduction or discontinuation of these drugs are permitted if required. And if safety problem was solved, it is possible to return the dosage to previous state.).

1) Antidepressants
2) Hypnotics (only ultrashort acting drugs [triazolam, zopiclone, zolpidem tartrate])
3) Non-steroidal anti-inflammatory drugs (except topical products for other than disease site of PHN)
4) Chinese herbal medicines with analgesic effects on neuropathic pain (life-preserving kidney-qi pill, peony and licorice decoction, eight-ingredient pill with rehmannia, etc.)

5.2.3 Rescue Medications

Acetaminophen will be permitted as a "rescue medication", to be used as needed only, and not to exceed the maximum dose stipulated in the package insert. Each subject should record dose(s) of acetaminophen used in the electronic patient diary from Visit 1 to Visit 10, if he/she takes acetaminophen.

5.2.4 Prohibited Concomitant Therapies

5.2.4.1 Prohibited Concomitant Therapies for Patients with DPNP

Concomitant use of the following therapies is prohibited from the screening (Visit 1) through post-treatment follow-up (Visit 11).

1) Nerve blocks
2) Laser therapy
3) Acupuncture treatment
4) Spinal cord stimulation
5) Surgery that might confound the assessment of DPNP
6) Electrical stimulation therapy
7) Other forms of pain reduction therapy that might confound the assessment of DPNP

5.2.4.2 Prohibited Concomitant Therapies for Patients with PHN

Concomitant use of the following therapies is prohibited from the screening (Visit 1) through post-treatment follow-up (Visit 11). After informed consent is obtained, subjects who are under treatment with the following prohibited concomitant thrapies will undergo a washout period of 7 days or more. Visit 1 will occur after completion of this washout period.

1) Nerve blocks
2) Iontophoresis
3) Laser therapy
4) Acupuncture treatment
5) Spinal cord stimulation
6) Surgery that may confound the assessment of PHN
7) Transcutaneous electrical nerve stimulation
8) Other forms of pain reduction therapy for PHN (except for psychological therapy, mental therapy, and physical therapy [eg, massage, kinesiology, heat treatment, and cryotherapy])

5.2.5 Restricted Concomitant Therapies for Patients with PHN

The following therapies are permitted for concomitant use if their frequency has not changed for 14 days prior to Visit 1. These drugs may be used concomitantly from the screening (Visit 1) through the post-treatment follow-up (Visit 11), but the dosage may not be changed.

1) Psychological therapy
2) Mental therapy
3) Physical therapy (eg, massage, kinesiology, heat treatment, and cryotherapy)

5.2.6 Other

Subjects should be instructed to avoid excessive consumption of alcohol during the treatment period, as the investigational product may increase side effects of sleepiness and dizziness and potentiate the impairment of motor skills.

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 to potential subjects. If it is felt that a subject is not able to adhere to the visit schedule, then that subject should not be enrolled into the study. Any missed visit that occurs during the this study must be rescheduled within 1 week.

6.1 Screening (Visit 1, 7 days prior to initiation of study treatment)

Written informed consent will be obtained before screening. For subjects with DPNP, if prohibited concomitant drugs are used within 7 days before obtaining informed consent, screening activities will follow a washout period of at least 7 days. For subjects with PHN, if prohibited concomitant drugs or prohibited concomitant therapies are used within 7 days before obtaining informed consent, screening activities will follow a washout period of at least 7 days. Therefore, in this case, written informed consent must be obtained before entering the washout period. The following activities and/or examinations will be performed at screening.

For patients with DPNP and patients with PHN:

- Evaluate inclusion criteria and exclusion criteria
- Record demographics (birth date, sex), medical/surgical history related to exclusion criteria and alcohol history
- Provide explanation regarding electronic patient diary, and provide electronic diary
- Complete SF-MPQ
- Complete HADS
- Measure body height and weight
- Perform physical examination
- Perform evaluation of edema
- Perform ophthalmologic examination
- Measure blood pressure and pulse rate

- Perform 12-lead ECG
- Collect blood and urine samples for laboratory tests
- Evaluate AEs
- Complete C-SSRS
- Perform pregnancy test (only in women of childbearing potential)
- Evaluate prior drug treatment, concomitant drugs, and concomitant therapy
- Complete Module A and B on MINI Interview (Version 6.0)

For patients with DPNP only:

- Record demographics specific for patients with DPNP (type of diabetes, duration of diabetes, duration of DPN, duration of DPNP)
- Perform full neurological examination
- Collect blood sample for evaluation of HbA1c
- Collect blood sample for evaluation of fasting blood glucose levels

For patients with PHN only:

- Record demographics specific for patients with PHN (site of herpes zoster skin rash, onset date and recovery date for current herpes zoster skin rash, duration of PHN, the site of PHN [trigeminal segment area, cervical segment area, thoracic segment area, lumbar segment area, and sacral segment area])

6.2 Initiation of Study treatment (Visit 2, Day 1)

At the beginning of the titration period, the following activities and/or examinations will be performed and 2.5 mg BID of DS-5565 will be issued to the subjects with moderate renal impairment (CrCL: 30-59 mL/min) or 2.5 mg QD of DS-5565 will be issued to the subjects with severe renal impairment (CrCL: 15-29 mL/min).

For patients with DPNP and patients with PHN:

- Evaluate inclusion criteria and exclusion criteria
- Review electronic patient diary data
- Complete SF-MPQ
- Complete HADS

- Measure body weight
- Perform physical examination
- Perform abbreviated neurological examination
- Measure blood pressure and pulse rate
- Collect blood and urine samples for laboratory tests
- Evaluate AEs
- Complete C-SSRS
- Record and evaluate concomitant drugs and concomitant therapy
- Issue the investigational product
- Select and record the drug administration in the morning (fasted/fed) during the study treatment (for only the subjects with moderate renal impairment)

For patients with PHN only:

- Perform full neurological examination

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.

For patients with DPNP and patients with PHN:

- Review electronic patient diary data
- Complete SF-MPQ
- Complete HADS
- Measure body weight
- Perform physical examination
- Perform abbreviated neurological examination
- Measure blood pressure and pulse rate

- Collect blood and urine samples for laboratory tests
- Evaluate AEs
- Complete C-SSRS
- 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
- Issue the investigational product
- Collect blood sample for PK analysis

6.3.2 Visit 5, Visit 6, Visit 7, Visit 8, and Visit 9

From Visit 4 to Visit 9, subjects will come to the study site once every 2 weeks (Visit 5, Visit 6, Visit 7, Visit 8, and Visit 9). 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, Visit 6, Visit 7, Visit 8, and Visit 9.

For patients with DPNP and patients with PHN:

- Review electronic patient diary data
- Complete SF-MPQ
- Complete HADS
- Measure body weight
- Perform physical examination
- Perform abbreviated neurological examination
- Measure blood pressure and pulse rate
- Collect blood and urine samples for laboratory tests
- Evaluate AEs
- Complete C-SSRS
- Record and evaluate concomitant drugs and concomitant therapy

- Collect unused investigational product, and record and review drug-taking compliance
- Issue the investigational product
- Collect blood sample for PK analysis (Visit 5 and Visit 6 only)

For patients with DPNP only:

- Collect blood sample for evaluation of HbA1c (Visit 6 only)
- Collect blood sample for evaluation of fasting blood glucose levels (Visit 6 only)

6.4 End of Treatment/Early Termination (Visit 10)

The treatment period will be completed at Visit 10. The following activities and/or examinations will be performed at the end of treatment/early termination.

For patients with DPNP and patients with PHN:

- Collect and review electronic patient diary data, and collect electronic diary
- Complete SF-MPQ
- Complete PGIC
- Complete HADS
- Measure body weight
- Perform physical examination
- Perform evaluation of edema
- Perform full neurological examination
- Perform ophthalmologic examination
- Measure blood pressure and pulse rate
- Perform 12-lead ECG
- Collect blood and urine samples for laboratory tests
- Complete C-SSRS
- 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

For patients with DPNP only:

- Collect blood sample for evaluation of HbA1c
- Collect blood sample for evaluation of fasting blood glucose levels

For patients with PHN only:

- Perform abbreviated neurological examination

6.5 Post-treatment Follow-up (Visit 11, 7 days after the completion of administration)

Follow-up observations will be conducted 7 days after the completion of administration (Visit 11). The following activities and/or examinations will be performed at post-treatment follow-up.

For patients with DPNP and patients with PHN:

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

7. EFFICACY ASSESSMENTS

7.1 Efficacy Variable(s)

1) Pain score[7]

Each subject will record a pain score in the electronic patient diary once daily from the day after Visit 1 through Visit 10. Every morning upon awakening, prior to taking study medication, the subject will select 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). ADPS is the weekly average pain score based on the pain scores from the electronic patient daily pain diaries.

2) Short-Form McGill Pain Questionnaire[8]

At Visit 1, Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, Visit 8, Visit 9, and Visit 10, 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

3) Patient Global Impression of Change[7]

At Visit 10, 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

4) 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. Each subject will record a sleep-interference score in the electronic patient diary once daily from the day after Visit 1 through Visit 10. 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 average sleep interference score is based on the sleep interference scores from the electronic patient daily pain diaries.

8. PHARMACOKINETIC AND BIOMARKER ASSESSMENTS

8.1 Pharmacokinetic Variable(s)

As part of this study, blood samples from subjects will be collected for PK analysis.

These blood samples will be collected at the following visits:

Visits 3, 4, 5 and 6 (Weeks 1, 2, 4 and 6)

Blood samples will be collected in accordance with the procedures described in Section 17.2.

8.1.1 For the Subjects with Moderate Renal Impairment

At the visits specified above, PK samples will be collected before the morning dose of study medication and 1 (± 0.5) hour after the morning dose. The subject will be instructed 1 visit before the scheduled visit for PK sampling not to take study medication before coming to the site.

In the CRF, the following will be recorded:

- Administration/No administration in the morning on the day before each visit
- Administration/No administration at bedtime on the day before each visit
- Administration/No administration in the morning on the day of each visit
- Date/Time of the morning dose on the day before each visit
- Date/Time of the bedtime dose on the day before each visit
- Date/Time of the morning dose on the day of each visit
- Taking/No taking breakfast on the day of each visit
- Date/Time of breakfast on the day of each visit
- Date/Time of blood sampling before the morning dose
- Date/Time of blood sampling 1 hour after the morning dose

8.1.2 For the Subjects with Sever Renal Impairment

At the visits specified above, PK samples will be collected 1 time.

In the CRF, the following will be recorded:

- Administration/No administration at bedtime on the day before each visit
- Date/Time of the bedtime dose on the day before each visit

- Date/Time of blood sampling

8.2 Biomarker Variable(s)

No biomarker analysis will be performed.

9. SAFETY ASSESSMENTS

Safety endpoints will be body weight, AEs, laboratory values, vital sign, 12-lead ECG, findings from physical examination, findings from neurological examination, C-SSRS, HADS, edema, and findings from ophthalmologic examination.

9.1 Adverse Events

9.1.1 Definition of Adverse Event

An AE is any unfavorable and unintended sign (including an abnormal laboratory value or abnormal vital sign), symptom, or disease that develops after the subject signs the Informed Consent Form (ICF) and up to 7 days after the last dose of study medication (Visit 11), regardless of relationship to the investigational product.

Any symptom that the investigator or sub-investigator considers associated with DPN 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. If any pre-existing symptom or disease is aggravated during the study period, the aggravation will be reported as an AE, and the date of confirming the aggravation will be considered the date of event onset.

Dizziness, somnolence, edema, and weight increase are currently defined as "significant AEs". Any other significant AEs to be added will be specified in the statistical analysis plan (SAP).

All antiepileptic drugs carry a risk of increased suicidal behavior and ideation. Furthermore, increased hepatic transaminases have been observed in the DS-5565 development program. Therefore, the following "suicidal behavior and ideation" and "liver enzyme elevations/liver dysfunction" will be treated as AEs of special interest.

- 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
- An elevation of ALT or AST $\geq 3 \times$ 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)

9.1.2 Items to Be Investigated Concerning Adverse Events

If an AE develops during the clinical study, the items in Table 9-1 will be investigated and the results will be recorded. The subject should be questioned in a general way, without asking about the occurrence of any specific symptoms.

Table 9-1: Items to be Investigated for Adverse Event

Items reviewed	Content of review	
Content of AE	Name of AE, date of onset	
Action taken regarding the investigational product	None	No change in investigational product dosage was made.
	Discontinued Permanently	The investigational product was permanently stopped.
	Interrupted	The investigational product was temporarily stopped.
	Dose Reduced	The dosage of the investigational products was reduced.
Outcome	Classification of outcome, date of outcome assessment, date of resolution	
Classification of outcome	Recovered/Resolved	• The subject fully recovered from the AE, with no residual effects observed.
	Recovered/Resolved with Sequelae	• The residual effects of the AE are still present and observable. • Identify sequelae/residual effects.
	Not Recovered/Not Resolved	• The AE itself is still present and observable.
	Recovering/Resolving	• The AE was almost fully resolved, and the subject recovered to near-baseline status.
	Unknown	• No information and the outcome was unknown.
	Fatal	
Severity	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
Seriousness	Serious (according to the following definition of SAEs) / Not serious	
Definition of SAE	1. Results in death 2. Life-threatening 3. Requires inpatient hospitalization or prolongation of existing hospitalization 4. Results in persistent or significant disability/incapacity 5. A congenital anomaly/birth defect 6. An important medical event	

Table 9-1: Items to be Investigated for Adverse Event (cont.)

Items reviewed	Content of review	
Relationship to the investigational product	Classification of relationship (in accordance with the following classifications of relationship), reason for that assessment	
Classification of relationship	Related	• The AE follows a reasonable temporal sequence from investigational product administration, and cannot be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, concomitant medications). • The AE follows a reasonable temporal sequence from investigational product 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 temporal sequence from investigational product administration, or can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, concomitant medications).
Other action taken for event	None	No treatment was required.
	Medication required	Prescription and/or over-the-counter 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	

SAE = serious adverse event

9.1.3 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).

9.1.4 Actions to Be Taken When Adverse Events Occur

When an AE occurs, the investigator or sub-investigator will provide appropriate treatment, will report the AE to the sponsor if necessary, and to the extent possible will monitor progress until the subject recovers or the AE is resolved or relieved. If it appears unlikely from a medical perspective that the subject will recover, this will be

explained to the subject, and monitoring of the subject as a part of the clinical trial will be concluded (although the treatment for the AE will be continued). In addition, clinical trial follow-up will be terminated and the clinical trial will be concluded if the investigator or sub-investigator decides further follow-up is unnecessary for the AE because there is no relationship between the AE and the investigational product, or if the subject refuses further follow-up.

9.2 Actions to Be Taken When Serious Adverse Events Occur

If a serious adverse event (SAE) occurs after obtaining the subject's written ICF and up to Visit 11, the investigator or sub-investigator will provide appropriate treatment for the subject and will report the event by phone or fax to the sponsor within 24 hours after becoming aware of the event. The investigator will promptly submit a detailed written report of the event to the sponsor. Written report of SAEs will be prepared and submitted to the head of the study site or to the Institutional Review Board (IRB), using the form and procedures specified by the study site. Detailed information regarding the procedures for reporting SAEs is provided separately, in the standard operating procedures for SAEs.

In addition, the following types of events should be reported to the sponsor within 24 hours after becoming aware of the event by phone or FAX:

- 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)
- 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 by phone or FAX.

- Severe hepatobiliary AE
- Hepatobiliary AE leading to discontinuation

- Any transaminase elevation associated with a clinical presentation suggestive of liver injury
- An elevation of ALT or AST ≥ 3 × ULN (without clinical presentation suggestive of liver injury)

9.3 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 investigational product. 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 to report any pregnancy in a subject using the Exposure In Utero (EIU) Reporting form. The investigator will contact the study monitor to obtain the EIU Reporting Form upon learning of a pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (ie, post-partum complications, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, including congenital anomaly in an aborted fetus), the investigator should follow the procedures for reporting SAEs.

9.4 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 9-2 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 9-2: 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, Visit 9, Visit 10, and Visit 11
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	
Pregnancy	Qualitative test (urine)	Visit 1 and Visit 10
HbA1c (only in patients with DPNP)	HbA1c	Visit 1, Visit 6, and Visit 10
Fasting blood glucose (only in patients with DPNP)	Fasting blood glucose level	Visit 1, Visit 6, and Visit 10

A/G ratio = albumin/globulin ratio CRP = C-reactive protein, LDH = lactate dehydrogenase, RBC = red blood cell, WBC = white blood cell

As described in Section 4.2.1, increases in aminotrasferases have been observed in the DS-5565 development program to date. Special monitoring of such elevations during Phase 3 is described below. The Hepatic Adjudication Committee (HAC) charter includes a process by which selected cases will be adjudicated by a liver disease specialist (Section 11.10). 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 $\geq 3 \times$ 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 4 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 $< 2 \times$ 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, special diets, and exposure to environmental chemical agents..
- Rule out alcoholic hepatitis; Nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Perform additional liver function tests (LFTs) (eg, serum lactate dehydrogenase [LDH], ALP, gamma-glutamyl transpeptidase, prothrombin time), evaluations for potential viral etiologies (including hepatitis A, B, C, E; cytomegalovirus; EBV) and autoimmune etiologies (anti-nuclear antibody, anti-smooth muscle antibody, anti-mitochondrial antibody).

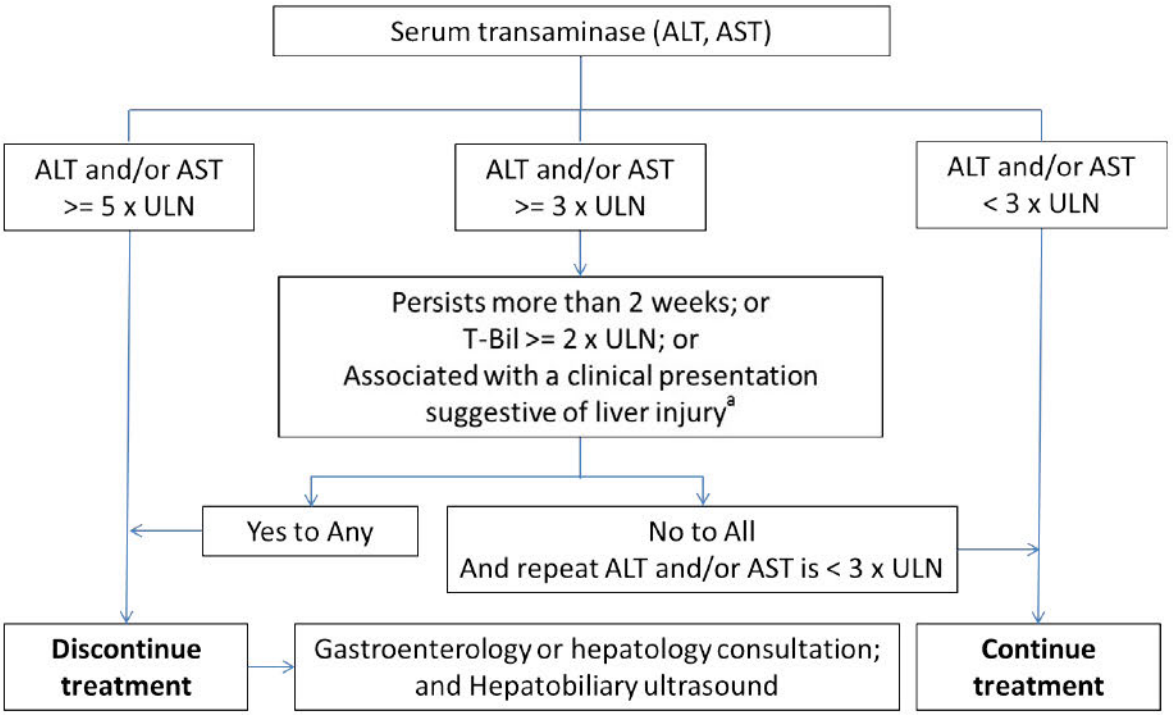
Combined elevations of aminotransferases and bilirubin meeting the criteria of a potential Hy's Law case [ALT or AST $\geq 3 \times$ ULN with simultaneous T-Bil $\geq 2 \times$ ULN], either serious or non-serious and whether or not causally related, should always be reported to the sponsor within 24 hours (refer to Section 9.2), with the investigator's assessment of seriousness, causality, and a detailed narrative. (Food Drug Administration [FDA]'s Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation; July 2009; http://www.fda.gov/downloads/Drugs/Guidance/UCM174090.). These events should

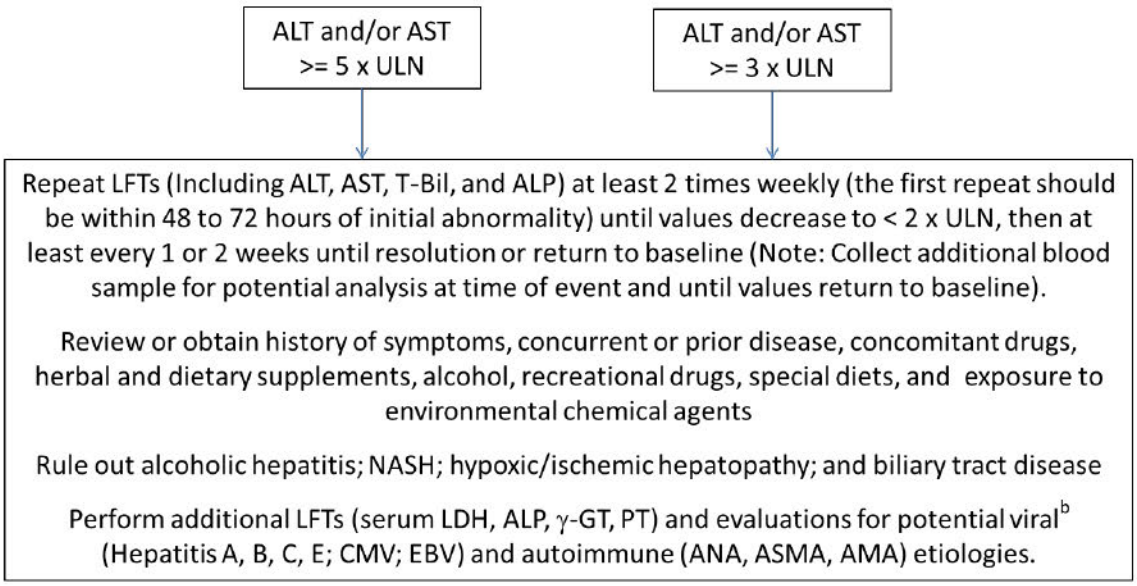
be reported as soon as possible following the procedures outlined in Section 9.2 for SAE reporting. The sponsor will be responsible for reporting the case(s) to the FDA.

Criteria for discontinuing subjects based on transaminase increases are provided in Section 4.2.1.

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

9.5 Vital Sign

Vital sign will be recorded at all visits and will include supine pulse rate and supine and orthostatic blood pressure. For measurement of supine blood pressure, subjects should be in a supine or semirecumbent position for at least 5 minutes before the blood pressure measurement. Measurement of orthostatic blood pressure should follow measurement of supine blood pressure. Subjects should be asked to stand for 3 minutes before measurement of orthostatic blood pressure. Measurement of blood pressure should be conducted using a calibrated manometer or automatic inflatable cuff monitor; the blood pressure cuff should be kept in place between supine and orthostatic blood pressure measurements. Results will be recorded in the CRF.

9.6 Electrocardiograms

At the stipulated times (Visit 1 and Visit 10), 12-lead ECG will be performed. Results (Normal/Abnormal, not clinically significant/Abnormal, clinically significant) will be recorded in the CRF.

9.7 Physical Findings

9.7.1 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.

9.7.2 Physical Examinations

At Screening Visit (Visit 1) and End of Treatment/Early Termination Visit (Visit 10), a complete physical examination, with the exception of pelvis, breast, and rectum in women and the genitourinary system and prostate in men, will be performed on each subject.

At Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, Visit 8, Visit 9, and Visit 11, the examination should minimally include clinical evaluations of the head, neck, thyroid, eyes, ears, nose, throat, heart, lungs, lymph nodes, abdomen, skin, extremities, and musculoskeletal system.

Results will be recorded in the CRF.

9.7.3 Evaluation of Edema

At Screening Visit (Visit 1) and Visit 10, evaluation of edema will be performed including physical examination and/or pitting. Results (presence or absence of edema and expression site) will be recorded in the CRF.

9.8 Other Safety Assessments

9.8.1 Neurological Examination for Patients with DPNP

This assessment will be performed only in patients with DPNP.

A full neurological examination will be performed at the stipulated times (Visit 1 and Visit 10). An abbreviated examination will be performed at Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, Visit 8, Visit 9, and Visit 11.

The full neurological examination will include the following: ankle jerk, vibratory sensation, pain sensation including hyperalgesia, allodynia, muscle strength (0-to-5 rating; ankle dorsiflexion), and gait/station (observation of regular walking, heel-to-toe [tandem] walking, and Romberg test, each assessed as normal or abnormal). The tests of ankle jerk, vibratory sensation, and pain sensation are detailed in the Procedures manual for the Diagnosis of Diabetic Peripheral Neuropathy and Neurological Examination. The assessment on pain symptom will be recorded as "Pain excepting tingling and pins & needles", "Tingling or pins & needles" or "Dysesthesia".

The abbreviated examination will include muscle strength and gait/station based on physical examination and medical interview, each assessed as normal or abnormal.

Results will be recorded in the CRF.

9.8.2 Neurological Examination for Patients with PHN

This assessment will be performed only in patients with PHN.

A full neurological examination will be performed at the stipulated times (Visit 2 and Visit 10). An abbreviated examination will be performed at Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, Visit 8, Visit 9, Visit 10 and Visit 11.

The full neurological examination will include the following: muscle strength (0-to-5 rating; ankle dorsiflexion), and gait/station (observation of regular walking, heel-to-toe [tandem] walking, and Romberg test, each assessed as normal or abnormal). The tests of the neurological examination are detailed in the Procedures manual for the Neurological Examination.

The abbreviated examination will include muscle strength and gait/station based on physical examination and medical interview, each assessed as normal or abnormal.

Results will be recorded in the CRF.

9.8.3 Ophthalmologic Examination

The ophthalmologic examination will be performed at Visit 1 (allowed to Visit 2) and Visit 10 (allowed to 4 days after). The examination includes examination of visual acuity and funduscopic examination. For a given subject, visual acuity should be examined under the same conditions (uncorrected or corrected) at both visits, and funduscopy should be performed with the same device. Results of visual acuity will be recorded as values, and results of funduscopic examination will be recorded as [Normal/Abnormal, not clinically significant/Abnormal, clinically significant] in the CRF.

9.8.4 Columbia-Suicide Severity Rating Scale[9]

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 or sub-investigator who has completed training prior to the study using the training DVD. The C-SSRS will be administered by the investigator or sub-investigator 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 4.2.3).

9.8.5 Hospital Anxiety and Depression Scale[10]

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. Results will be recorded in the CRF.

9.8.6 Pregnancy test

Pregnancy tests (urine tests) will be conducted at the stipulated times (Visit 1 and Visit 10), 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

No other assessments will be performed.

11. STATISTICAL METHODS

11.1 Objective

The primary objective is to characterise the safety and tolerability of DS-5565 in subjects with moderate to severe renal impairment. The secondary objectives including the efficacy are shown in section 2.1.2.

11.2 General Statistical Considerations

The statistical package SAS® (Version 9.2 or higher) will be used to produce tables, figures, and listings.

Safety analysis set will be used for all safety and efficacy analyses and PK analysis set will be for all PK analyses. All analyses will be conducted by CrCL group (ie, moderate and severe renal function impaired patients group).

Missing weekly ADPS value will be imputed based on “nonfuture dependence" model using the pattern mixture approach under the missing not at random (MNAR) mechanism[11-13] so that bad outcomes (greater weekly ADPS value) can be attributed to subjects who discontinued the trial before Week 14. Detail will be at Section 11.5.2.1and in the SAP.

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.

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 1 post-randomization value.

PK analysis will be detailed in the PK analysis plan (PAP).

A detailed SAP and PAP describing the methodology to be used in the final analysis will be prepared before data unblinding. 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 and PAP.

11.3 Analysis Sets

The safety analysis set will include all subjects who signed the ICF and received at least 1 dose of study medication.

The PK analysis set will include all subjects who signed the ICF and received a dose of DS-5565 and had at least 1 PK sample collected.

11.4 Study Population Data

Demographic and baseline characteristics will be summarized for the safety and PK analysis sets.

11.5 Efficacy Analyses

11.5.1 Primary Efficacy Analyses

Not applicable.

11.5.2 Secondary Efficacy Analyses

All efficacy analyses will be performed using the safety analysis set. The summary statistics and/or frequency tables will be provided by CrCL group at each week or scheduled visit. No hypothesis testing will be conducted for all efficacy endpoints.

11.5.2.1 Average Daily Pain Score

Observed weekly ADPS and change from baseline will be summarized by CrCL group and week.

Missing weekly ADPS values will be imputed based on a multiple imputation (MI) method using "nonfuture dependence" model which is specified by the pattern mixture approach with shifting parameters under MNAR mechanism[11-13]. The imputation method above will consider the reason for dropout together with the time of dropout for constructing the missing data pattern.

The statistical model used for the MI data generation will be the Markov Chain Monte Carlo method with adjustment for covariates (eg, age, sex) to produce a monotone pattern first, and then the imputation will continue using the Regression with Predictive Mean Matching method for the monotone pattern with the same set of covariates. The primary shifting parameter values corresponding to the three categories in the pattern mixture model 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)*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 residual SD at first missing week after imputation. The imputed value will be replaced with 10 (the maximal ADPS score) when the imputed value of ADPS score is over 10. Additionally, for dropouts due to LOE, the imputed values will be bound so that a subject's imputed weekly ADPS after discontinuation cannot be better than that subject's baseline ADPS. Each complete imputed dataset will be analyzed using the repeated measures analysis with week as the fixed effect, week as the repeated effect, and baseline ADPS as a covariate to provide LS mean in weekly ADPS at each week. The results of the analysis from each complete imputed dataset will be combined using Rubin's rule.

Sensitivity analyses will include following:

- Repeated measures analysis using observed data only
- ANCOVA using Baseline Observation Carried Forward
- ANCOVA using LOCF

11.5.2.2 Responder Rate for Averaged Daily Pain Score

ADPS responder rate, defined as the proportion of subjects with ≥ 30% and ≥ 50% reduction from baseline to Week 14, will be calculated. The cumulative distribution of reduction from baseline in ADPS will be provided as a continuous responder analysis[14].

11.5.2.3 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.

11.5.2.4 Patient Global Impression of Change

PGIC score will be described as frequency table.

11.5.2.5 Sleep-Interference Score

The summary statistics will be computed for the ADSIS and the change from baseline at each week.

11.6 Pharmacokinetic/Biomarker Analyses

11.6.1 Pharmacokinetic Analyses

Scatter plot illustrating the pharmacokinetic relationship between time after dose and plasma concentration by renal function for each visit will be created, using the PK

analysis set. The population PK analysis will be reported separately from the clinical study report (ie not in the clinical study report).

11.6.2 Biomarker Analyses

Not applicable.

11.7 Safety Analyses

11.7.1 Adverse Event Analyses

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AEs that appear after the first administration or that worsen relative to the pre-treatment state are considered as TEAEs.

The number and percentage of subjects reporting TEAEs will be calculated for the categories listed below by CrCL group and all-DS-5565 treatment. The number and percentage of subjects reporting TEAEs and ADRs will be summarized by system organ class, preferred term, and CrCL group and all-DS-5565 treatment.

- TEAE
- ADR
- Serious TEAE
- Serious ADR
- Severe TEAE
- Severe ADR
- Significant TEAE
- Significant ADR
- TEAE leading to treatment discontinuation
- ADR leading to treatment discontinuation

11.7.2 Clinical Laboratory Evaluation Analyses

For the hematology and blood chemistry test parameters, summary statistics will be calculated for the measured values and change from baseline at each scheduled visit. A shift table will be created based on the categories of "abnormal low", "normal", and "abnormal high" between baseline and each scheduled visit.

Additionally, for ALT, AST, T-Bil, and ALP, the number and percentage of subjects who meet the criteria specified in FDA Drug-Induced Liver Injury guideline[15] and evaluation of drug-induced serious hepatotoxicity plot will be provided. For the urinalysis parameters excepting specific gravity, the number and percentage of subjects will be provided at each visit. Summary statistics will be tabulated for the specific gravity. A shift table will be created based on the categories of "normal" and "abnormal" between baseline and each scheduled visit.

11.7.3 Vital Sign Analyses

Summary statistics will be calculated for measured values and changes from baseline in the supine and orthostatic blood pressure, and supine pulse rate at each scheduled visit.

11.7.4 Electrocardiogram Analyses

A shift table will be provided for ECG evaluation between baseline and Visit 10.

11.7.5 Physical Finding Analyses

Summary statistics will be calculated for measured values and changes from baseline in body weight at each scheduled visit. For the evaluation of edema, the results (presence or absence) will be tabulated for each expression site.

11.7.6 Columbia-Suicide Severity Rating Scale

The data collected from C-SSRS will be tabulated.

11.7.7 Hospital Anxiety and Depression Scale

The subscales of anxiety and depression for HADS will be summarized at each scheduled visit.

11.7.8 Other Safety Analyses

The data collected from the ophthalmologic examination will be tabulated at each scheduled visit.

11.8 Other Analyses

Not applicable.

11.9 Data Safety Monitoring Board

An independent DSMB will be responsible for reviewing unblinded safety data in an ongoing manner and for monitoring and assuring overall safety of the study subjects. In accordance with an agreed-upon charter, the DSMB will meet periodically, on a regular

and/or ad hoc basis, to discuss and address any emerging safety or tolerability issues, including SAEs, discontinuations due to AEs, etc, as well as other relevant study information, such as recruitment status, ineligibility rates, and data quality. Based on any formal DSMB review meeting where blinded or unblinded safety data are reviewed and discussed, the DSMB will recommend to the sponsor one of the following:

- Continue the study without modification
- Continue the study but modify the protocol and/or ICF
- Suspend the study (or a cohort) until further notice, with recommendations for further action to address specific issues and appropriately managing active study subjects
- Terminate the study (or a cohort) with provisions for orderly discontinuation in accordance with GCP.

Modification, suspension or termination may be made for any of the following reasons:

- Concern about drug-induced liver injury
- Concern about suicide
- Any other safety concern

The approach to study (or cohort) modification, suspension, or termination will be described in the DSMB charter.

The sponser will be notified of the DSMB's decision soon after the meeting. Minutes of all formal DSMB meetings and discussions will be maintained by the independent statistician, in a secure location, until completion or termination of the study, at which point they will be forwarded to Daiichi Sankyo for archiving.

11.10 Hepatic Adjudication Committee

The HAC will comprise at least two qualified hepatologists, who are not investigators in the study and not otherwise directly associated with the sponsor. The HAC will follow its own charter for processing and adjudicating hepatic events. The HAC will adjudicate hepatic events in a blinded manner. This adjudication will be independent of the investigators. The HAC will complete assessments on an ongoing basis. Adjudication of hepatic events will be based on evaluation of eCRFs and source documents, as available, including but not limited to hospital discharge summaries, diagnostic imaging, histopathology, consultation, and laboratory reports. Such patient's

relevant records will be provided to the HAC from the study sites according to HAC request.

11.11 Sample Size Determination

Approximately 35 subjects with moderate and severe renal dysfunction will be enrolled in the study.

We need 30 subjects to observe at least 1 AE of moderate/severe dizziness and somnolence with 95% probability if the event rate is assumed to be 10%, which is nearly double of observed proportion in the Asian DPNP Phase 2 study (DS5565-A-J202). Considering dropout, total of approximately 35 subjects will be enrolled into the study.

12. DATA INTEGRITY AND QUALITY ASSURANCE

The investigator/study site will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

12.1 Monitoring and Inspections

The monitor 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 monitor is responsible for visiting study site(s) at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to International Conference on Harmonization (ICH) GCP and local regulations on the conduct of clinical research. The monitor is responsible for inspecting the CRFs and ensuring completeness of the essential study documents. The monitor should have access to subject medical records and other study-related records needed to verify the entries in the CRFs.

The monitor will communicate deviations from the protocol, standard procedures, GCP, and applicable regulations to the investigator and will ensure that appropriate action designed to prevent recurrence of the detected deviations is taken and documented.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed and documented.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from the sponsor. Inspection of site facilities (eg, pharmacy, drug storage areas, laboratories, etc.) and review of study-related records will be performed in order to evaluate the conducting of the study and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

12.2 Data Collection

12.2.1 Style of Data Collection

12.2.1.1 Case Report Form

This study will use an Electronic Data Capture (EDC) system (Table 12-1) to generate CRFs, so the CRFs will be entered electronically. CRFs (including audit trails) will be

prepared for each subject. The eCRF will be completed, reviewed, and e-signed by the investigators. The EDC system will be validated prior to use.

Table 12-1: Electronic Data Capture System

Name of EDC system	Medidata Rave®
EDC system developer	Medidata Solutions Inc.
Entry method	Web-based data entry
Input terminal	Desktop computer at the study site
Incompatible operating systems	None
Recommended browsers	The Medidata Rave® supports any browser which is HTML 4, HTML 5, and CSS2 compliant. Browsers must have JavaScript enabled.
Screen Resolution	The minimum screen resolution required to properly display Medidata Rave applications is 1024 × 764.
Connection Speed	128kbps is the minimum connection speed recommended for using Medidata Rave.
Other	Adobe Flash Player : ver. 10 or above is required

12.2.1.2 Electronic Daily Diary

This study will use an Electronic Patient Report Outcome (ePRO) system (Table 12-2) to collect patient daily diary data. The device for electronic daily diaries (including audit trails) will be prepared for each subject. The electronic daily diaries will be completed by the patient and reviewed by the investigators. The ePRO system will be validated prior to use.

Table 12-2: Electronic Patient Report Outcome System

EDC system developer	eResearchTechnology, Inc
Entry method	Patient-reported outcomes; Hand-held device
Input terminal	DIARYpro® Mobile
Incompatible operating systems	None
Recommended browsers	DIARYpro® Mobile is a proprietary system that runs on a Windows platform. Windows OS and Internet Explorer 7.0. 8.0, 9.0,10.0 or 11.0
Screen Resolution	N/A, as software is programmed to fit on the DIARYpro mobile device.

12.2.1.3 Other Reports

Results of pharmacokinetic test and laboratory tests are reported by central laboratory, separately. Procedures for these reports are set separately.

12.2.2 Preparation of Case Report Forms and Daily Diaries

All persons who make entries and/or corrections on CRFs or daily diaries should be trained and should be assigned their own accounts to use the EDC or ePRO system. The training record is regarded as a signature sheet.

1. CRFs will be created for subjects who sign the ICF for the study, and electronic daily diaries will be created for subjects who are conducted screening visit for the study.
2. The investigator or sub-investigator will prepare the CRF in accordance with CRF completion guidelines that are provided by the sponsor.
3. If study staff assists in the preparation of the CRF, they will do so under the direction of the investigator or sub-investigator.
4. The investigator will submit the CRF to the sponsor, and will keep a copy.
5. If there is a contradiction between some of the data that is entered in the CRF and the source documents, the investigator will prepare a separate record that explains the reason(s) for this discrepancy, and will submit that record to the sponsor.
6. Subject will receive the device for the electronic daily diaries and answer to the question.
7. The device for the electronic daily diaries should be collected when subject terminate

the study.

12.2.3 Signatures or Seals on the Case Report Form

The investigator will confirm all of the CRFs that are prepared at that study site, and will enter his or her electronic signature in the file.

The investigator will also confirm all of the electronic daily diaries that are prepared at that study site.

12.2.4 Data Correction

1. The investigator, sub-investigator, or study staff will correct the data in the CRF in accordance with the CRF completion guidelines that are provided by the sponsor.
2. The investigator will be responsible for the content of entries in the CRF.
3. Procedure for data correction of the electronic daily diariys will set separately.

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 electronically and/or manually as appropriate. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, data will be reviewed for adherence to the protocol and GCP. For eCRFs and ePRO 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 or ePRO applications and also resolved within the applications.

Data received from external sources such as central labs 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.

12.4 Study Documentation and Storage

12.4.1 Definition of Source Documents

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, electronic diaries, microfiches, X-rays, and correspondence.

If the following items are entered directly into the CRF, the content of those CRF entries is defined as source data.

1) Direct entry of specific items (in the Comments column, etc.)
2) Entries such as "None" or "Unknown" for specific items
3) Reasons for use of concomitant drugs
4) Laboratory values that deviated from the reference range, if any, and reason for deviation.
5) Descriptions of AEs
6) AEs, if any, name of AE, severity, seriousness, outcome, relationship to the investigational product
7) Whether treatment was discontinued, and reason for discontinuation

12.4.2 Storage

All original source documents supporting entries in the eCRFs and electronic daily diary must be maintained and be readily available.

All essential documentation will be retained by the institution for at least 10 years after completion of the study (for a longer period if needed to comply with other applicable requirements), or until the institution is instructed otherwise by the sponsor.

No study document should be destroyed without prior written agreement between the 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 the sponsor in writing of the new responsible person and/or the new location.

12.5 Record Keeping

Records of subjects, source documents including electronic daily diary, monitoring visit logs, data correction forms, CRFs, inventory of investigational product, regulatory documents (eg, protocol and amendments, IRB 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.

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 or the contract research organization (CRO) in charge of monitoring. This agreement will include the financial information agreed upon by the parties.

13.2 Reimbursement, Indemnity, and Insurance

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

14. PUBLICATION POLICY

1. [redacted]

2. [redacted]

15. STUDY ADMINISTRATIVE INFORMATION

15.1 Compliance Statement, Ethics, and Regulatory Compliance

The study will be conducted in compliance with the provisions set forth in Articles 14-3 and 80-2 of the Pharmaceutical Affairs Law, and Ordinance on Standards for Conduct of Clinical Trials of Drugs, Ministry of Health, Labor and Welfare Ordinance No. 28, dated 27 March 1997 (GCP Ordinance, hereinafter). The rights, well-being, and safety of subjects will be protected to the utmost extent in adherence to the ethical principles of the Declaration of Helsinki.

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 regulations.

The investigator must ensure that the subject's anonymity is maintained. On the CRFs or other documents submitted to the sponsor or a 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 ICFs) 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, the regulatory agency(ies), and the IRB 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 Procedures

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 investigational products are administered.

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 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.

Suggested model text for the ICF for the study is provided in the sponsor's ICF template for the investigator to prepare the documents to be used at his or her site. Updates to applicable forms will be communicated from the sponsor.

15.4 Regulatory Compliance

The study protocol, subject information and consent form, the Investigator's Brochure, any written instructions to be given to the subjects, 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 IRB for ethical review and approval according to 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 investigator must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the ICF. The investigator should notify the 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 procedures.

As required by regulations, the sponsor's Regulatory Affairs group or representative to whom this responsibility has been delegated will ensure that all legal aspects are covered, that approval from the appropriate regulatory bodies is obtained prior to study initiation, and that changes to the initial protocol and other relevant study documents are implemented only after approval by the relevant regulatory bodies.

15.5 Protocol Deviations

The investigator should conduct the study in compliance with the protocol, which was agreed to by the sponsor and, if required, by the regulatory authorities, and which was approved or given a favorable opinion by the IRB.

A deviation to eliminate an apparent immediate hazard to one or more subjects may be implemented immediately. The sponsor and the IRB must be notified.

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

The investigator should notify the IRB of deviations from the protocol in accordance with 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, IRBs, and regulatory authorities of that information, and when needed, will amend the protocol and/or subject information.

The investigator should immediately inform the subject orally 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 in the medical records, for example, and the subject's willingness to remain in the study should be confirmed.

If the subject information is revised, it must be re-approved by the 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 orally. The subject and the investigator or other responsible personnel who provided explanations should sign and date the revised ICF.

15.7 Duration of the Study

Study duration (from first patient in [FPI] to last patient last visit LPLV): January 2016 to May 2017

15.8 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. Also, the sponsor will assure the timely submission of amendments to regulatory authorities.

A global protocol amendment will affect study conduct at all sites in all regions of the world. Such amendments will be incorporated into a revised protocol document. Changes made by such amendments will be documented. 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). Such amendments generally will not be incorporated into a revised protocol document. Changes made by such amendments will be clearly stated in a document separate from the protocol. Sponsor approval of local amendments will be clearly documented.

A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for subject safety. In the case of immediate implementation, the situation must be documented and reported to the IRB within five working days.

15.9 Study Discontinuation or Suspension

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.

15.10 Organization

15.10.1 Sponsor

Daiichi Sankyo Co., Ltd.
3-5-1 Nihonbashi-honcho, Chuo-ku, Tokyo 103-8426, Japan
PPD
PPD

15.10.1.1 Sponsor's Responsible Medical Expert

PPD

PPD

PPD

PPD

15.10.1.2 Sponsor's Responsible Medical Adviser

PPD

PPD

PPD

PPD

15.10.1.3 Study Representative

PPD, Vice President, Clinical Development Department, R&D Division

15.10.1.4 Clinical Study Lead

PPD, Clinical Development Department, R&D Division

15.10.1.5 Delivery Lead

PPD, Clinical Development Department, R&D Division

Daiichi Sankyo Co., Ltd.

1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan

PPD

PPD

15.10.1.6 Person Responsible for Study Drug Management

PPD CMC Planning Department

15.10.1.7 Person Responsible for Biostatistical Analysis

PPD, Biostatistics & Data Management Department

15.10.1.8 Person Responsible for Pharmacokinetic Analysis

PPD Translational Medicine & Clinical Pharmacology Department

15.10.1.9 Person Responsible for Modeling & Simulation

PPD Translational Medicine & Clinical Pharmacology Department

15.10.1.10 Person Responsible for Concentration Measurement

PPD Translational Medicine & Clinical Pharmacology Department

15.10.1.11 Person Responsible for Study Data Management

PPD Clinical Data and Biostatistics Department

15.10.1.12 Person Responsible for Quality Control

PPD , Development Function

15.10.1.13 Person Responsible for Evaluation of Safety Information

PPD Pharmacovigilance Department

15.10.1.14 Person Responsible for Measure of Safety Information

PPD Pharmacovigilance Department

15.10.1.15 Person Responsible for GCP Audit

PPD R&D & PV Quality Assurance Department

15.10.2 Academic Research Organization

Not applicable

15.10.3 Contract Research Organization

15.10.3.1 Contract Research Organization in Charge of Monitoring

CMIC Co., Ltd.
1-1-1 Shibaura, Minato-ku, Tokyo 105-0023, Japan
PPD
PPD

15.10.3.2 Contract Research Organization in Charge of Interactive Web Response System

PPD
Bell Medical Solutions. Inc.
Tokyu Bldg. East No.3, 2-16-8 Minami-Ikebukuro, Toshima-ku, Tokyo 171-0022, Japan
PPD

15.10.3.3 Contract Research Organization in Charge of Emergency Contact

Bell Medical Solutions. Inc.
Tokyu Bldg. East No.3, 2-16-8 Minami-Ikebukuro, Toshima-ku, Tokyo 171-0022, Japan
PPD
PPD

15.10.4 Central Laboratory

15.10.4.1 Bioanalytical Laboratory

Celerion

621 Rose Street, Lincoln, NE 68502 USA

PPD

PPD

15.10.4.2 Central Laboratory Management

SRL Medisearch Inc.

6-5-1 Nishishinjuku, Shinjuku-ku, Tokyo 163-1310, Japan

PPD

PPD

15.10.4.3 Central Laboratory

SRL, Inc.

2-1-1 Nishishinjuku, Shinjuku-ku, Tokyo 163-0409, Japan

PPD

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15.10.5 Data Safety Monitoring Board

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15.10.6 Contract Research Organization in Charge of Data Safety Monitoring Board Coordination

MMS Holdings, Inc.

6880 Commerce Blvd, Canton, MI 48187, USA

PPD

PPD

15.10.7 Hepatic Adjudication Committee

PPD

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15.10.8 Contract Research Organization in Charge of Hepatic Adjudication Committee Coordination

MMS Holdings, Inc.

6880 Commerce Blvd, Canton, MI 48187, USA

PPD

PPD

15.10.9 EDC System Development

Medidata Solutions, Inc.

PPD

350 Hudson Street, 9th Floor, New York, NY 10014, USA

PPD

PPD

Role: They will be responsible for the operation management and maintenance of the EDC system in accordance with a business trust agreement.

15.10.10 EDC System Support

Fujitsu Systems East Limited

PPD

Shinagawa season terrace, 1-2-70 Konan, Minato-ku, Tokyo 108-0075, Japan

PPD

PPD

Role: They will be responsible for the EDC System Support in accordance with a business trust agreement.

15.10.11 ePRO system Development and Support

eResearchTechnology, Inc

PPD

PPD

PPD

Role: They will be responsible for the operation management, maintenance of the ePRO system and ePRO System Support in accordance with a business trust agreement.

16. REFERENCES

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17. APPENDICES

17.1 Schedule of Events

Table 17-1: Study Visits

	Screening	Intiation of study treatment	Treatment period							End of Treatment	Post-treatment follow-up	Early Termination
Visit	1	2	3	4	5	6	7	8	9	10	11	
Week	−1	0	1	2	4	6	8	10	12	14	15	
Day	≤ −7	1	8	15	29	43	57	71	85	99	Day 7 post-last-dose	
Visit window (days)	−7 to −14	–	6 to 10	13 to 17	26 to 32	40 to 46	54 to 60	68 to 74	82 to 88	96 to 102	Day 5 to 14 post-last-dose	
Informed consent	X[a]											
Inclusion/exclusion criteria	X	X										
Demographic information	X											
Medical /surgical history	X											
Efficacy parameter(s) - see next table for details	X	X	X	X	X	X	X	X	X	X		X
Body height and weight	X	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X
Evaluation of edema	X									X		X
Full neurological examination	X[c]	X[d]								X		X
Abbreviated neurological examination		X	X	X	X	X	X	X	X	X[d]	X	X[d]
Ophthalmologic examination	X[e]									X[f]		X
Vital sign	X	X	X	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	X	X	X

	Screening	Intiation of study treatment	Treatment period							End of Treatment	Post-treatment follow-up	Early Termination
Visit	1	2	3	4	5	6	7	8	9	10	11	
Week	−1	0	1	2	4	6	8	10	12	14	15	
Day	≤ −7	1	8	15	29	43	57	71	85	99	Day 7 post-last-dose	
Visit window (days)	−7 to −14	–	6 to 10	13 to 17	26 to 32	40 to 46	54 to 60	68 to 74	82 to 88	96 to 102	Day 5 to 14 post-last-dose	
HbA1c[c)]	X					X				X		X
Fasting blood glucose[c)]	X[e)]					X				X		X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X
HADS	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test	X									X		X
AE reporting	◄											►
Prior and concomitant medication and therapy	X	X	X	X	X	X	X	X	X	X	X	X
Investigational product dispensing		X	X	X	X	X	X	X	X			
Selection of Investigational product dose timing		X										
Investigational product compliance			X	X	X	X	X	X	X	X		X
PK sampling			X	X	X	X						
MINI (only Module A and B)	X											

a: For patients with DPNP: After informed consent is obtained, subjects who are under treatment with prohibited concomitant medications (see 5.2.1) will undergo a washout period of 7 days or more.
For patients with PHN: After informed consent is obtained, subjects who are under treatment with prohibited concomitant medications or prohibited concomitant therapies (see 5.2.1) will undergo a washout period of 7 days or more.
b: Body weight only.
c: These will be performd for patients with DPNP only.
d: These will be performed for patients with PHN only.
e: These will be performed between Visit 1 and Visit 2.
f: These will be performed between Visit 10 and 4 days after Visit 10.

Table 17-2: Efficacy Assessment by Visit

	Screening	Initiation of study treatment	Treatment period							End of Treatment	Post-treatment follow-up	Early Termination
Visit	1	2	3	4	5	6	7	8	9	10	11	
Week	−1	0	1	2	4	6	8	10	12	14	15	
Day	≤ −7	1	8	15	29	43	57	71	85	99	Day 7 post-last-dose	
Visit window (days)	−7 to −14	–	6 to 10	13 to 17	26 to 32	40 to 46	54 to 60	68 to 74	82 to 88	96 to 102	Day 5 to 14 post-last-dose	
Pain diaries	←	—	—	—	—	—	—	—	—	→		X
Sleep interference diaries	←	—	—	—	—	—	—	—	—	→		X
SF-MPQ	X	X	X	X	X	X	X	X	X	X		X
PGIC										X		X

17.2 Processing of Blood Samples for Pharmacokinetic Analyses

Blood samples for PK analysis should be taken by venipuncture at time points detailed in Section 6 and Table 17-1. Blood should be collected into Vacutainer tubes containing K2 EDTA as anticoagulant for the preparation of plasma. It is important to fill the Vacutainer tubes to the specified collection volume. The tube containing blood for plasma preparation should be gently inverted multiple times (at least 9) to ensure thorough mixing of anticoagulant and blood, and then immediately placed in a cool box containing ice-water. The samples should be centrifuged within 30 minutes after collection, at approximately 1500 g and approximately +4°C for approximately 10 minutes. Immediately following centrifugation, the separated plasma for each sample should be divided into two aliquots of at least 0.5 mL. The aliquots of plasma should each be pipetted into a polypropylene cryogenic sample storage vial (at least 2–3 mL in size, with screw-cap) with appropriate information (barcode and/or subject identification code, date, time and aliquot number). The aliquots must be kept chilled for the entire time until they are transferred to the freezer. Each set of aliquots should be stored in separate boxes. Within 60 minutes after blood draw, the sample storage vials should be stored in the dark in a -20°C (-15°C to -30°C) freezer. Any sample anomalies should be recorded on the sampling forms.

The samples at the study sites will be collected by the central laboratory.

Detailed shipping instructions and addresses will be provided with the site laboratory manual.