CLINICAL STUDY PROTOCOL

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED SAFETY STUDY OF DS-5565 FOR TREATMENT OF PAIN DUE TO FIBROMYALGIA IN SUBJECTS WITH CHRONIC KIDNEY DISEASE

DS5565-A-U307

IND 118,304
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SPONSOR:	Daiichi Sankyo Pharma Development 399 Thornall Street Edison, NJ 08837 United States
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INVESTIGATOR AGREEMENT

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED SAFETY STUDY OF DS-5565 FOR TREATMENT OF PAIN DUE TO FIBROMYALGIA IN SUBJECTS WITH CHRONIC KIDNEY DISEASE

Sponsor Approval:

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

PPD	PPD
Print Name	**Signature**
Associate Director, Clinical Development	14 March 2017
Title	**Date (DD MMM YYYY)**

Investigator's Signature:

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

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

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International 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**

PROTOCOL SYNOPSIS

EudraCT/IND Number:	EudraCT 2014-003972-21/IND 118,304
Protocol Number:	DS5565-A-U307
Investigational Product:	DS-5565
Active Ingredient(s)/INN:	[(1R,5S,6S)-6-(Aminomethyl)-3-ethylbicyclo[3.2.0]hept-3-en-6-yl]acetic acid monobenzenesulfonate/mirogabalin
Study Title:	A Randomized, Double-Blind, Placebo-Controlled Safety Study of DS-5565 for Treatment of Pain Due to Fibromyalgia in Subjects with Chronic Kidney Disease
Study Phase:	Phase 3
Indication Under Investigation:	Fibromyalgia (FM)
Study Objectives:	The primary objective is: • To determine the safety and tolerability of subjects with FM and moderate to severe renal dysfunction during 13 weeks of renally adjusted dosing of DS-5565 compared to placebo. The secondary objectives are: • To compare change in weekly average pain as assessed by average daily pain score (ADPS) from baseline measured at randomization to Week 13 in subjects receiving either dose of DS-5565 versus placebo. Weekly ADPS is based on daily pain scores reported by the subject that best describes the worst pain over the previous 24 hours • To assess the effects of DS-5565 on patient global impression of change (PGIC) at Week 13/ET.
Study Design:	This is a stratified, randomized, double-blind, placebo-controlled, multi-center safety study of DS-5565 in subjects with FM and renal dysfunction. Eligible subjects will be randomized 2:1 to receive either DS-5565 7.5 mg once daily (QD) or placebo for the category of subjects with

	creatinine clearance (CrCl) 15-29 mL/min, or 2:1 to receive treatment with DS-5565 7.5 mg twice daily (BID) or placebo for the category of subjects with CrCl 30-59 mL/min. Subjects will be stratified for renal impairment by CrCl. The treatment period is 13 weeks in duration.
Study Duration:	The total study duration (individual subject) will be approximately 21 weeks. The study includes a screening period (approximately 3 weeks but no longer than 35 days, including a washout period [if necessary] and a 1-week baseline period), double-blind treatment period (13 weeks), and a 4 week follow-up period.
Study Sites and Location:	Approximately 100 sites in the US (United States), Europe, and other countries will participate in the study.
Planned Sample Size:	Approximately 60 subjects will be randomized. Assuming a 25% dropout rate, approximately 45 subjects will complete the double-blind treatment period. This sample size is thought to be sufficient to address the objectives of this clinical trial.
Subject Eligibility Criteria:	Inclusion Criteria: 1. Age ≥ 18 years 2. Able to give written informed consent 3. Able to complete patient-reported questionnaires per the Investigator's judgment 4. Estimated CrCl between 15-59 mL/min from serum creatinine by the central laboratory using the Cockcroft-Gault equation 5. Fibromyalgia meeting American College of Rheumatology criteria for FM: a. Widespread pain index (WPI) ≥ 7 and symptom severity (SS) scale score ≥ 5, or WPI 3 to 6 and SS scale score ≥ 9, b. Pain in at least 11 of 18 specific tender point sites, c. Symptoms have been present at a similar level for at least 3 months, and d. The subject does not have a disorder that would otherwise explain the pain 6. ADPS of ≥ 4 on the 11-point numeric rating scale

(NRS) over the 7 days prior to randomization (based on completion of at least 4 daily pain assessments during the 7-day baseline period prior to randomization)

7. Women of child bearing potential (WOCBP) must be using adequate methods of contraception (as detailed in Section 4.1.3) to avoid pregnancy during the study and for 4 weeks after study completion.

Exclusion Criteria:

1. Need for ongoing use of concomitant chronic pain medications or any new non-pharmacological pain management techniques that may confound assessments of efficacy and/or safety, including neurolytic treatments (destruction of nerves by chemicals, heat, cold) or surgery, intrathecal pumps, spinal cord stimulators or psychological support within the previous year. Also excluded: topical capsaicin within 6 months; or systemic corticosteroids within 3 months of baseline period.
2. Unable to undergo pre-study washout of prohibited concomitant medications
3. Subjects with recent history (i.e., within 1 year prior to screening) of alcohol abuse or illicit drug use (cocaine, heroin, marijuana [including medical, prescribed], etc.)
4. Use of any selective serotonin reuptake inhibitor (SSRI), unless the subject has been on a stable dose for $\geq$ 90 days prior to screening and is not anticipated to need any dose adjustment during the course of the study
5. Subjects with severe or uncontrolled depression that, in the judgment of the Investigator, makes the subject inappropriate for entry into the study
6. Significant neurological or psychiatric disorder unrelated to neuropathic pain
7. Other severe pain (eg, sciatica, rheumatoid arthritis) that might impair the assessment of neuropathic pain
8. CrCl $\geq$ 60 mL/min estimated from serum creatinine by the central laboratory using the Cockcroft-Gault equation.

9. Subjects who are on hemodialysis or who require hemodialysis before the follow-up assessment; acute renal failure; history of kidney transplant
10. Any history of a malignancy other than basal cell carcinoma within the past 5 years
11. Clinically significant unstable neurologic, ophthalmologic, hepatobiliary, respiratory, or hematologic illness or unstable cardiovascular disease (eg, severe hypotension, uncontrolled cardiac arrhythmia, or myocardial infarction) within 12 months prior to screening
12. Pregnancy or breast feeding or intent to become pregnant during the study period
13. Known hypersensitivity to $\alpha_2\delta$ ligands or other components of the study medications. Note: Prior exposure to DS-5565 is allowed, as long as hypersensitivity to DS-5565 was not observed.
14. Clinically significant ECG abnormalities at the Screening Visit
15. Subjects who are at risk of suicide, as defined by their responses to the C-SSRS or in the opinion of the Investigator. Note: Subjects answering "yes" to any of the C-SSRS questions must be excluded. Such subjects should be referred immediately to a mental health professional for appropriate evaluation.
16. Subjects with current severe or uncontrolled major depressive disorder or anxiety disorders as assessed by the Mini-international Neuropsychiatric Interview (MINI) interview (Version 6.0) at screening, or who answer “yes” to the suicidality question (current or past) on the Major Depressive Episode Module (Module A) or who answer “yes” to any question in the Suicidality Module (Module B) are excluded. Subjects with mild to moderate major depression or anxiety disorders are permitted to enroll provided that the investigator assesses the subject as clinically stable and appropriate for entry into the study.
17. Subjects who are unlikely to comply with the protocol (eg, uncooperative attitude, inability to return for subsequent visits, and/or otherwise

considered by the Investigator to be unlikely to complete the study)

18. Subject is currently enrolled in, or it has been fewer than 30 days since ending, another investigational device or drug study or is receiving another investigational agent.
19. Subjects who are employees or immediate family of employees of the study site, Sponsor, or contract research organization (CRO)
20. Screening laboratory values outside the limits listed in the table below:

Hematology	Hemoglobin	< 8 g/dL
	Platelet count	< 100,000/mm^3
	Absolute neutrophil count	< 1,500/mm^3
Blood chemistry	AST	> 2.0 × ULN
	ALT	> 2.0 × ULN
	Alkaline phosphatase	> 1.5 × ULN
	Total bilirubin	> 1.2 × ULN[a]
	Creatine kinase	> 3.0 × ULN
	Calculated CrCl	≥ 60 mL/min

[a] If a subject has total bilirubin > ULN: unconjugated and conjugated bilirubin fractions should be analyzed and only subjects documented to have Gilbert's syndrome may be enrolled.
Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, CrCl = creatinine clearance (determined by the central laboratory using the Cockcroft-Gault equation), ULN = upper limit of normal

Dosage Form, Dose and Route of Administration:	Study medications will be provided in blister cards ("wallets"). DS-5565 will be supplied in the form of 7.5 mg tablets for oral administration. Doses of DS-5565 include 7.5 mg QD and 7.5 mg BID. Matching placebo tablets are also used.
Study Endpoints:	The primary safety objective is the safety and tolerability of

renally adjusted doses of DS-5565 versus placebo.

Specific safety endpoints assessed include:

- All treatment-emergent adverse events (TEAEs)
- Change in clinical laboratory evaluations from baseline measured at randomization to Week 13/ET for DS-5565 versus placebo
- Change in neurological examinations from baseline to Week 13/ET for DS-5565 versus placebo
- Change in electrocardiograms from baseline to Week 13/ET for DS-5565 versus placebo
- Change in Columbia-Suicide Severity Rating Scale (C-SSRS) from baseline to Week 13/ET for DS-5565 versus placebo
- Assessment of Physician Withdrawal Checklist (PWC).

The secondary efficacy endpoints include:

- Changes in ADPS from baseline measured at randomization to Week 13/ET for DS-5565 versus placebo. Weekly ADPS is based on daily pain scores reported by the subject that best describes the worst pain over the previous 24 hours.
- Proportion of subjects with improvement in overall status at Week 13/ET as assessed by PGIC for DS-5565 versus placebo.

Statistical Analyses:

Primary Endpoint

The primary objective is the safety and tolerability of DS-5565. Safety data will be summarized by treatment group. 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.

Secondary Endpoint

The secondary efficacy endpoints will be summarized by treatment and numerically compared between treatment groups.

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
$\alpha_2\delta$	Alpha-2 Delta
ADPS	Average Daily Pain Score
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Concentration-Time Curve
BID	Twice Daily
CFR	Code of Federal Regulations
CKD	Chronic Kidney Disease
CL/F	Total Clearance
CLr/F	Renal Clearance
C_{max}	Maximum Plasma Concentration
CNS	Central Nervous System
CrCl	Creatinine Clearance
CRF	Case Report Form
CRO	Contract Research Organization
CSPV	Clinical Safety and Pharmacovigilance
C-SSRS	Columbia-Suicide Severity Rating Scale
DPNP	Diabetic Peripheral Neuropathic Pain
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ESRD	End Stage Renal Disease
EIU	Exposure In Utero
ET	Early Termination
FDA	Food and Drug Administration

ABBREVIATION	DEFINITION
FM	Fibromyalgia
GCP	Good Clinical Practice (refers to ICH and CFR)
HAC	Hepatic Adjudication Committee
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INN	International Non-proprietary Name
IRB	Institutional Review Board
IXRS	Interactive Voice/Web Response System
LS	Least Squares
MedDRA	Medical Dictionary for Regulatory Activities
M.I.N.I	Mini-international Neuropsychiatric Interview
NRS	Numeric Rating Scale
PD	Pharmacodynamic
PGIC	Patient Global Impression of Change
PHN	Post-Herpetic Neuralgia
PK	Pharmacokinetic
QD	Once Daily
RBC	Red Blood Cell
PWC	Physician Withdrawal Checklist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAVER	Serious Adverse Event Report
SD	Standard Deviation
SF-MPQ	Short Form-McGill Pain Questionnaire
SID	Subject Identification Number
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SOP	Standard Operating Procedure
SS	Symptom Severity
SSRI	Selective Serotonin Reuptake Inhibitor
SUSAR	Suspected Unexpected Serious Adverse Reaction

ABBREVIATION	DEFINITION
$t_{1/2}$	Terminal Elimination Half-Life
TEAE	Treatment-Emergent Adverse Event
ULN	Upper Limit of Normal
US	United States
USA	United States of America
VAS	Visual Analog Scale
WBC	White Blood Cell
WHO	World Health Organization
WOCBP	Women of Child-Bearing Potential
WPI	Widespread Pain Index

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Investigational Product(s)

1.1.1. Name

DS-5565 is the compound code for [(1R,5S,6S)-6-(Aminomethyl)-3-ethylbicyclo[3.2.0] hept-3-en-6-yl]acetic acid monobenzenesulfonate/mirogabalin.

1.1.2. Description

DS-5565 is a potent and specific ligand of the alpha$_2$-delta ($\alpha_2\delta$) subunit of voltage-dependent calcium channels in the central nervous system (CNS). The $\alpha_2\delta$ subunit has been identified as the molecular target for the analgesic effects of pregabalin and gabapentin, two currently marketed drugs for the treatment of chronic neuropathic pain, thus establishing an important therapeutic target for pain control.[1]

1.1.3. Intended Use Under Investigation

DS-5565 is being developed as treatment for diabetic peripheral neuropathic pain (DPNP), fibromyalgia (FM), and post-herpetic neuralgia (PHN).

1.1.4. Nonclinical Studies

DS-5565 has been evaluated in animal models of neuropathic pain and has been found to be as effective as or more effective than pregabalin. Preclinical evaluations have demonstrated a favorable safety profile supporting chronic dosing in humans.

DS-5565 was assessed in intermittent cold stress mice, an experimental animal model for FM, and demonstrated a significant and sustained analgesic effect. Nonclinical evaluations have demonstrated a favorable safety profile supporting chronic dosing in humans.

Data from nonclinical studies of DS-5565 are summarized in the DS-5565 Investigator Brochure.

1.1.5. Clinical Experience

Sixteen Phase 1 clinical pharmacology studies of DS-5565 and two Phase 2 studies of DS-5565 in subjects with DPNP have been completed. Additionally, a global phase 3 effort is underway in patients with pain due to fibromyalgia. Approximately, 3600 subjects will be randomized into three identical studies, each lasting approximately 20 weeks. Approximately half of those subjects (1800) will be exposed to up to 30 mg DS5565 daily (placebo and pregabalin treatment arms will also be employed).

Following oral administration to healthy volunteers in these Phase 1 studies, DS-5565 was rapidly absorbed and maximum plasma concentration (C_{max}) was achieved at approximately 1 h. Following a single administration of DS-5565, C_{max} and area under the concentration-time curve (AUC) increased almost proportionally with dose level,

from 3 mg through 75 mg. Negligible accumulation was noted following twice daily (BID) administration of DS-5565. Terminal elimination half-life ($t_{1/2}$) was approximately 4 h to 7 h following BID administration of DS-5565. The majority of A200-0700, the free form of DS-5565, is excreted in urine unchanged. Recently, a food effect study was conducted at the target clinical dose of 15 mg using the final formulation and indicated that food did not significantly affect the total exposure (AUC) of A200-0700. However, C_{max} of A200-0700 was decreased by approximately 18% under fed conditions when compared with that under fasted conditions.

The overall exposure to DS-5565, based on AUC, increased with severity of renal impairment. As assessed using the geometric least square (LS) means ratios, exposure was approximately 1.4-, 2.0-, 4.0-, and 5.0-fold greater for subjects with mild, moderate, and severe renal impairment and end-stage renal disease (ESRD), respectively, compared to subjects with normal renal function. Apparent clearance and renal clearance of DS-5565 decreased with increasing severity of renal impairment.

DS-5565 did not affect the pharmacokinetics (PK) of ethanol, lorazepam, zolpidem, tramadol, or metformin in healthy subjects. The PK of DS-5565 was not significantly affected by those compounds.

In a ^{14}C-labeled DS-5565 mass balance study in healthy subjects given a single oral dose of 30 mg, the mean total radioactivity recovered in urine and feces was 96.85% and 1.21% of the administered dose, respectively. In a thorough QT study, there were no clinically significant changes in 12-lead electrocardiogram (ECG) parameters; neither the therapeutic dose (15 mg of DS-5565) nor the supratherapeutic dose (50 mg of DS-5565) affected cardiac repolarization.

In the United States (US), one Phase 2 study (DS5565-A-U201) in subjects with DPNP was completed. In the DS5565-A-U201 study, LS mean differences versus placebo in change in average daily pain score (ADPS) from baseline to Week 5 were -0.22, -0.53, -0.94, -0.88, and -1.01 for the DS-5565 5 mg once daily (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 pregabalin 150 mg BID did not significantly differentiate from placebo in ADPS or proportion of responders at end point. A second Phase 2 study with a similar design (DS5565-A-J202) was completed in Asia (Japan, Korea, and Taiwan). In the DS5565-A-J202 study, LS mean differences versus placebo in change in ADPS from baseline to Week 7 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 not statistically significant.

DS-5565 has been shown to be well tolerated at single doses up to 30 mg. The most frequently reported treatment-emergent adverse events (TEAEs) have been CNS-related events (eg, dizziness and somnolence) that are expected based on the mechanism of action of DS-5565. Most reported TEAEs were judged to be mild or moderate, and most were considered to be related to the study drug. In the completed Phase 2 studies, all DS-5565 dose levels (from 5 mg QD to 15 mg BID) were generally well tolerated.

Additional data from clinical studies of DS-5565 are summarized in the DS-5565 Investigator's Brochure.

1.2. Study Rationale

Several classes of medications, including anticonvulsants, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors (SNRIs), and opioids are used to treat the symptoms of FM, with variable efficacy, safety, and tolerability. Currently available $\alpha_2\delta$ ligands, gabapentin and pregabalin, are established as effective treatments for pain associated with diabetic peripheral neuropathy.[2,3] In addition they are approved for the treatment of pain in FM in the USA and some other countries, however not in the EU (European Union). The dosage, and thus efficacy, of these agents are limited by frequent and significant CNS-related side effects, including dizziness and somnolence; associated weight gain and peripheral edema can also be problematic.[4] As a result, a large proportion of patients with FM are left with insufficient pain relief and new treatment options are needed.

DS-5565 is an oral analgesic drug being developed by Daiichi Sankyo for DPNP, FM, and PHN, globally. This study is being conducted in patients with chronic renal dysfunction and pain due to fibromyalgia solely, after receiving guidance from the US FDA. DS-5565 binds to the $\alpha_2\delta$ subunit of voltage-dependent calcium channels, the main target for the analgesic effect of pregabalin and gabapentin. Nonclinical and Phase 1 and Phase 2 clinical data support the progress of DS-5565 into Phase 3 studies of FM to evaluate the effect of DS-5565 on ADPS as compared to placebo during the course of a 13-week (stable dose, not including 1 week of titration for the DS-5565 15 mg BID group) double-blind treatment period.

DS-5565 has been studied in subjects with renal dysfunction. Study DS5565-A-E106 evaluated the pharmacokinetics and safety of a single 5 mg dose in 40 subjects (8 normal renal function and 8 each with mild, moderate, severe, and ESRD requiring hemodialysis). Pharmacokinetics of DS-5565 and its lactam metabolite were evaluated over a 72-hour period. For the analysis, the groups were analyzed by normal creatinine clearance (CrCl) ($\geq$ 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 as per the FDA Draft Guidance, *Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling*.[5]

The PK analysis indicated that there was a significant reduction in both renal clearance (CLr/F) and total clearance (CL/F) of DS-5565 and its lactam metabolite as renal function decreased.

In order to test the safety and tolerability of DS-5565 in subjects with renal dysfunction, the doses (7.5 mg BID for subjects with CrCl between 30-59 mL/min and 7.5 mg QD for subjects with CrCl between 15-29 mL/min) are predicted to produce exposures similar to those in subjects with normal renal function at 15 mg BID.

DS-5565 is a next-generation $\alpha_2\delta$ ligand being developed as a potent analgesic with an anticipated wider therapeutic margin than pregabalin, separating optimal efficacy and

side effects. The present study aims to evaluate the safety and efficacy of DS-5565 for treating pain in subjects with FM with chronic kidney disease.

1.3. Risks and Benefits for Study Subjects

The results from nonclinical studies suggest that subjects treated with DS-5565 may experience improvement in pain associated with FM. The clinical efficacy of DS-5565 has been evaluated in two Phase 2, multi-center, randomized, double-blind, and placebo- and active-comparator controlled adaptive studies in subjects with DPNP. In the first study (conducted in the US), the 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. These data provide proof-of-concept for DS-5565 as a treatment for DPNP. The second Phase 2 study was similarly designed and conducted in Asia (Japan, South Korea and Taiwan). The DS-5565 5 mg BID, 10 mg BID, and 15 mg BID treatment groups did not demonstrate statistically significant mean reductions in ADPS; however, trends favoring DS-5565 over placebo were evident in some secondary efficacy endpoints, including mean reductions in visual analog scale (VAS) for Short Form-McGill Pain Questionnaire (SF-MPQ) given at the highest dose.

DS-5565 is cleared from the body primarily via the kidneys. In order to test the safety and tolerability of DS-5565 in subjects with renal dysfunction, the doses (7.5 mg BID for subjects with CrCl between 30-59 mL/min and 7.5 mg QD for subjects with CrCl between 15-29 mL/min) are predicted to produce exposures similar to those in subjects with normal renal function at 15 mg BID. Previous studies of subjects with renal dysfunction suggested the need for reducing the dose in those subjects with either moderate or severe impairment of renal function.

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. 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. These risks are unknown in subjects with chronic kidney disease (CKD). DS-5565 is currently being studied in a global phase 3 program in patients with pain due to FM.

A full description of safety data related to DS-5565, including the results of Phase 1 and Phase 2 clinical studies of DS-5565, is provided in the DS-5565 Investigator Brochure. Safety monitoring procedures described in the protocol are considered to be adequate to protect subject safety.

1.4. Population, Route, Dosage, Dosage Regimen, Treatment Period

The study population will be adult (age $\geq$ 18 years) male and female subjects with a CrCl between 15-59 mL/min, and a diagnosis of FM for up to 5 years prior to screening.

Subjects must meet specific pain criteria at the Screening and Randomization Visits for inclusion. Full details regarding eligibility criteria are provided in Section 4.

The dosage form of DS-5565 drug product is white oval 7.5 mg tablets. The tablet formulation includes DS-5565 drug substance, mannitol, carboxymethylcellulose calcium, magnesium stearate, and Opadry®OY-S-9607 (a pre-mixed powder for coating suspension containing hypromellose, titanium dioxide, and talc). The tablets will be orally administered. Study treatment may be taken with or without food once in the morning and once in the evening. Matching placebo tablets will also be used.

Full details regarding study treatment are provided in Section 5.

1.5. Compliance Statement, Ethics, and Regulatory Compliance

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Conference on Harmonisation (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s) including:

- Food and Drug Administration (FDA) GCP Regulations: Code of Federal Regulations (CFR) Title 21, parts 11, 50, 54, 56, and 312 and/or
- European Commission Directive (2001/20/EC Apr 2001) and/or
- European Commission Directive (2005/28/EC Apr 2005) as appropriate.

1.5.1. Subject Confidentiality

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

The Sponsor will observe the rules laid down in the European Data Protection Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and the free movement of such data.

The Investigator must ensure that the subject's anonymity is maintained. On the Electronic Case Report Forms (eCRF) or other documents submitted to the Sponsor or designee, subjects should be identified by a unique subject identifier as designated by the Sponsor. Documents that are not for submission to the Sponsor or designee (eg, signed Informed Consent Forms [ICF]) should be kept in strict confidence by the Investigator.

In compliance with applicable regulations and ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the Sponsor, of the regulatory agency(s), and the Independent Ethics Committee (IEC) or Institutional Review Board (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.

1.5.2. Informed Consent Procedure

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 screening procedures or any study drugs are administered. The written ICF should be prepared in the local language(s) of the potential subject population.

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

The subject's written informed consent should be obtained prior to his/her participation in the study and should be documented in the subject's medical records, as required by law. 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 or legal representative. 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 and any applicable subparts are provided in the Sponsor ICF template for the Investigator to prepare the documents to be used at his or her site. Updates to applicable forms will be communicated via letter from the Sponsor.

Additional consent is required for the Health Insurance Portability and Accountability Act (HIPAA) only in the USA.

1.5.3. Regulatory Compliance

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

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the Statistical Analysis Plan (SAP).

The Investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document or changes of the investigational site, facilities, or personnel. The Investigator should notify the IRB/IEC of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from the Sponsor or designee, in accordance with local procedures.

As required by local regulations, the Sponsor's local Regulatory Affairs group will insure all legal aspects are covered and approval of the appropriate regulatory bodies obtained, prior to study initiation, and that implementation of changes to the initial protocol and other relevant study documents happen only after the appropriate notification of or approval by the relevant regulatory bodies.

2. STUDY OBJECTIVES AND HYPOTHESES

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective is to determine the safety and tolerability of subjects with FM and moderate to severe renal dysfunction during 13 weeks of renally adjusted dosing of DS-5565 compared to placebo.

2.1.2. Secondary Objectives

The secondary objectives of this study are:

- To compare change in weekly average daily pain as assessed by ADPS from baseline measured at randomization to Week 13/ET in subjects receiving either dose of DS-5565 versus placebo. Weekly ADPS is based on daily pain scores reported by the subject that best describes the worst pain over the previous 24 hours
- To assess the effects of DS-5565 on patient global impression of change (PGIC) at Week 13/ET.

2.2. Study Hypothesis

The hypothesis of this Phase 3 study is that doses of 7.5 mg BID of DS-5565 in subjects with CrCl between 30-59 mL/min and 7.5 mg QD of DS-5565 in subjects with CrCl between 15-29 mL/min DS-5565 will be safe and well tolerated.

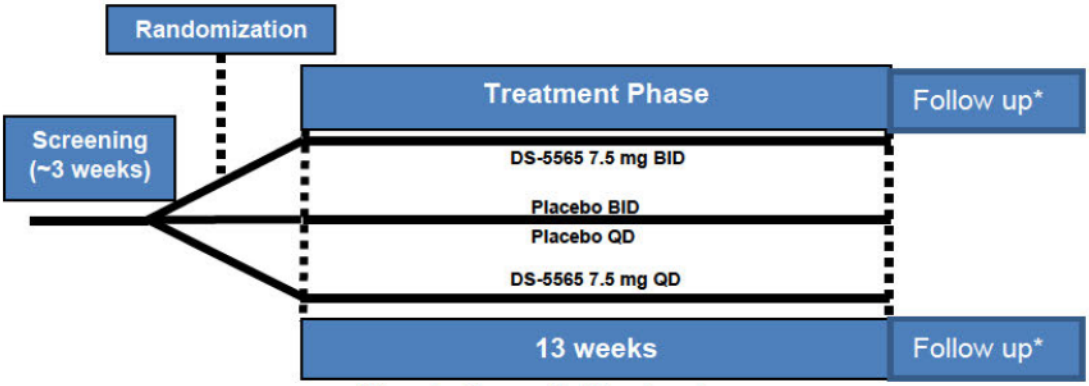
3. STUDY DESIGN

3.1. Overall Plan

3.1.1. Study Type

This is a stratified, randomized, double-blind, placebo-controlled, multi-center safety study of DS-5565 for the treatment of pain due to FM in subjects with CrCl between 59 and 15 mL/min. The study design is depicted in Figure 3.1.

Figure 3.1: Design of Phase 3 Study of DS-5565 in Subjects with FM



*4 weeks from end-of-treatment
Abbreviations: BID = twice daily, QD = once daily

3.1.2. Treatment Groups

Subjects who meet all eligibility criteria will be randomized 2:1 to receive either DS-5565 7.5 mg QD or placebo for the category of subjects with CrCl 15-29 mL/min, or 2:1 to receive treatment with DS-5565 7.5 mg BID or placebo for the category of subjects with CrCl 30-59 mL/min.

Matching placebo will be utilized to conduct the double-blind treatment period.

The Schedule of Events is listed in Section 17 and the Study Procedures in Section 6.

3.1.3. Study Endpoints

The primary safety endpoint is the safety and tolerability of renally adjusted doses of DS-5565 versus placebo.

Specific safety endpoints assessed include:

- All treatment-emergent adverse events (TEAEs)
- Change in clinical laboratory evaluations from baseline measured at randomization to Week 13/ET for DS-5565 versus placebo
- Change in neurological examinations from baseline to Week 13/ET for DS-5565 versus placebo
- Change in electrocardiograms from baseline to Week 13/ET for DS-5565 versus placebo
- Change in Columbia-Suicide Severity Rating Scale (C-SSRS) from baseline to Week 13/ET for DS-5565 versus placebo
- Assessment of Physician Withdrawal Checklist (PWC) at follow-up visits.

The secondary efficacy endpoints include:

- Changes in ADPS from baseline measured at randomization to Week 13/ET for DS-5565 versus placebo. Weekly ADPS is based on daily pain scores reported by the subject that best describes the worst pain over the previous 24 hours.
- Proportion of subjects with improvement in overall status at Week 13/ET as assessed by PGIC for DS-5565 versus placebo.

3.1.4. Duration of the Study

3.1.4.1. Duration of Subject Participation

The total study duration (for individual subject's participation) will be approximately 21 weeks. The study includes a screening period (approximately 3 weeks but no longer than 35 days, including a washout period [if necessary] and a 1-week baseline period), double-blind treatment period (13 weeks), and a 4 week follow-up period.

3.1.5. Stopping Rules

3.1.5.1. Stopping Rules for Individual Subjects

For any subject discontinued from the study based on one of the stopping rules outlined in Section 3.1.5.1.1, the associated event must be reported as an adverse event (AE) or serious AE (SAE) in the eCRF within 24 hours of awareness. Please refer to Section 9.4 for further instructions.

3.1.5.1.1. Elevations of Aminotransferases

Although a mechanism- or metabolism-based potential for drug-induced liver injury has not been established for DS-5565, instances of increased hepatic transaminases have been observed during the development program. In addition, acetaminophen, an agent known to cause liver injury (due to saturation of its metabolism when overdosed), is commonly used in this population and is included in this study as an allowed treatment for pain. As such, a standardized approach for stopping rules and careful monitoring of serum transaminases is considered prudent. Stopping rules for elevation in serum transaminases are included as a general precaution, with attention to FDA guidance for detection and assessment of drug-induced liver injury premarketing clinical evaluations, and are described below. Specific recommendations regarding monitoring of subjects with elevations are described in Section 9.3.2.

Subjects with any of the following elevations in aminotransferases should be discontinued from treatment and followed closely, as noted above.

- Increase in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\geq$ 5 x upper limit of normal (ULN)
- ALT or AST increases to $\geq$ 3 x ULN and persists for more than 2 weeks
- Concurrent increases in ALT or AST $\geq$ 3 x ULN and total bilirubin $\geq$ 2 x ULN
- ALT or AST $\geq$ 3 x ULN associated with a clinical presentation suggestive of liver injury (i.e., including the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia)

3.1.5.2. Suicidal Behavior and Ideation

The $\alpha_2\delta$ ligand class of medications has been associated with increased risk of suicidal thoughts or behavior (Section 9.3.1). Two separate cases of completed suicide were observed in the Phase 2 DS5565-A-J202 study.

The C-SSRS and Mini-international Neuropsychiatric Interview (MINI) (Version 6.0) are to be administered at any time during the study (including unscheduled visits) where the investigator/study coordinator/site staff recognizes or become aware of (and this includes if this awareness arises during unscheduled visits or non-face-to-face communications with the patient or his/her family):

- Any suggestion of mood disturbance and/or any awareness of a potential suicidal risk,

- Substantial changes in their psychosocial environment (ie, the death of or separation of close family/friend, sudden financial burden, worsening of medical condition, etc); in this case administration of the C-SSRS/MINI and consultation with a psychiatrist (onsite preferably) should be performed.

In this study, the C-SSRS will be administered at all clinic visits. Based on the C-SSRS and Investigator judgment, if a subject is identified as being at risk for suicide, appropriate safety measures should be implemented, including:

- A subject should be discontinued from the study, and immediately referred to a mental health professional for further evaluation, if a 'YES' response has been recorded for any question on the C-SSRS at any visit (current or past), unless the subject falls into the 'Possible Exception' category below.
  - Possible Exception (with regard to a 'YES' response(s) to C-SSRS Q1 and/or Q2 only):

1. The benefit from continuation on the study medication significantly outweighs the risk of continuing the subject on study drug. Such cases need to be discussed with the sponsor medical director and should take into account the mental health professional evaluation AND
2. The justification for continuing the subject in the study under these circumstances is to be appropriately documented per study procedure

Subjects should be discontinued from the clinical study and immediately referred to a mental health professional (preferably an onsite psychiatrist evaluation if possible) if subjects are assessed as having current severe or uncontrolled major depressive disorder or anxiety disorders by the MINI at any visit (current or past) and if any of the following conditions apply:

- The investigator determines that there is a suicidality risk, irrespective of any scales or
- Any "Yes" response to:
  - MINI questions
    - Module A (Major Depressive Disorder) question A3, G or
    - Any question on Module B (Suicidality) or
  - Relevant C-SSRS questions, with discontinuation criteria as outlined above.

3.1.5.3. Decreased CrCl Below Minimum

If at any time during the study the CrCl drops below 15 mL/min, the subject must be discontinued from the study utilizing the stated withdrawal procedures and referred to a nephrologist.

3.1.5.4. Stopping Rules for the Study

Circumstances under which the study may be stopped based upon independent Data and Safety Monitoring Board (DSMB) recommendation are specified in Section 11.9. In addition, the study may be terminated at any time at the Sponsor's discretion.

3.2. Selection of Doses

3.2.1. Experimental Treatments for the Study

Dose regimens were selected based on results of single-dose studies in healthy volunteers, as well as dose optimization modeling and simulation. At doses from 3 to 75 mg, DS-5565 was rapidly absorbed, with a median time to maximum plasma concentration (t_{max}) of approximately 1 hour. Mean $t_{1/2}$ ranged from approximately 3 hours to 5 hours, and C_{max} and AUC appeared to increase proportionally with doses from 3 mg through 75 mg. The majority of administered DS-5565 is excreted in the urine (approximately 61% to 77% of the dose). The overall exposure to DS-5565, based on AUC, increased with severity of renal impairment.

In the completed Phase 2, randomized, double-blind, placebo- and pregabalin-controlled study of DS-5565 in subjects with DPNP in the US (DS5565-A-U201), the primary efficacy endpoint was met. Greater mean decreases from baseline to end-of-treatment (Week 5) in ADPS were observed in the DS-5565 treatment groups compared to placebo. The mean changes from baseline to Week 5 (with last observation carried forward imputed for missing values) in ADPS were -2.0, -2.3,
-2.7, -2.6, and -2.8 for the DS-5565 5 mg QD, 10 mg QD, 15 mg QD, 10 mg BID, and 15 mg BID treatment groups, respectively. By comparison, placebo and pregabalin showed mean changes of -1.9 and -1.8, respectively.

DS-5565 has been shown to be generally well-tolerated at single doses up to 30 mg. The most frequently reported TEAEs are CNS-related events that are expected based on the mechanism of action of DS-5565 and included high rates of dizziness and somnolence. Most reported TEAEs were judged to be mild or moderate, and most were considered to be related to the study drug. In the completed Phase 2 study (DS5565-A-U201), all DS-5565 dose levels were generally well tolerated.

DS-5565 has been studied in subjects with renal dysfunction. Study E106 evaluated the PK and safety of a single 5 mg dose in 40 subjects (8 subjects with normal renal function and 8 subjects each with mild, moderate, severe, and ESRD, respectively). Pharmacokinetics of DS-5565 and its lactam metabolite were evaluated over a 72-hour period. For the analysis, the groups were analyzed by normal CrCl ($\geq$ 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).

The PK analysis indicated that there was a significant reduction in both CLr/F and CL/F of DS-5565 and its lactam metabolite as renal function decreased (Table 3.1).

Table 3.1: Renal and Total Clearance of DS-5565 and its Lactam Metabolite with Decreasing Renal Function

CrCL (mL/min)	N	CL/F (L/hr)	
		Observed Median (Min, Max)	Predicted Median (Min, Max)
≥ 90	6	20.0 (12.7, 23.2)	18.9 (10.7, 22.9)
60-89	8	17.4 (8.94, 20.5)	17.2 (9.28, 19.5)
30-59	10	8.04 (6.90, 11.3)	8.01 (7.21, 11.2)
15-29	4	4.73 (3.80, 5.75)	4.81 (3.83, 5.95)
<15	4	3.76 (2.75, 5.98)	3.87 (2.82, 5.76)

CrCl = creatinine clearance; CL/F = total clearance

In subjects with moderate and severe renal dysfunction BID doses of 7.5 mg and QD dosing of 7.5 mg are expected to produce exposures equivalent to a BID doses of 15 mg in subjects with normal renal function (Table 3.2).

Table 3.2: Predicted DS-5565 AUC with Daily and Twice Daily Doses of 7.5-15 mg in Renal Dysfunction

CrCl Group (mL/min)	Dose	$AUC_{ss,0-24h}$ (ng*h/mL)		$C_{max,ss}$ (ng/mL)	
		Mean	Median	Mean	Median
≥ 90	15 mg BID	1834	1590	241	252
60-89	15 mg BID	1958	1747	238	226
30-59	7.5 mg BID	1754	1873	161	152
15-29	7.5 mg QD	1586	1563	157	165

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

3.2.1.1. Experimental Treatment for Individual Subjects

There will be no dose adjustments.

3.2.2. Control Treatments

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

4. STUDY POPULATION

4.1. Enrollment

Investigators will maintain a confidential screening log of all potential study candidates that includes limited information of the subjects (initials, age, sex) date and outcome of screening process (eg, enroll in the study, reason for ineligibility, refused to participate).

Prior to initiation of formal screening procedures, each subject will be asked to review and sign the ICF provided by the site. All subjects must personally sign and date the ICF before any study-specific activities occur. For additional information on informed consent, see Section 1.5.2.

Each subject will be assigned a unique subject identification number (SID) upon signature of the ICF at the Screening Visit. The SID will be an 8-digit number with the first 4 digits corresponding to the site number and the last 4 digits as sequentially assigned by the interactive voice/web response system (IXRS). The SID will be used to identify the subject throughout the study and will be entered on all study documentation. If a subject discontinues from the study at any time, his/her SID cannot be reassigned to another subject.

Investigators will maintain a confidential subject identification code list. This confidential list of names of all subjects allocated to study numbers on enrolling in the study allows the Investigator to reveal the identity of any subject when necessary.

A subject will be considered enrolled upon being randomized into the study. Investigators will maintain an enrollment log of all subjects enrolled in the study, indicating their assigned study number.

4.1.1. Inclusion Criteria

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

1. Age ≥ 18 years
2. Able to give written informed consent
3. Able to complete patient-reported questionnaires per the Investigator's judgment
4. Estimated CrCl between 15-59 mL/min from serum creatinine by the central laboratory using the Cockcroft-Gault equation
5. Fibromyalgia meeting American College of Rheumatology criteria for FM:
    a. Widespread pain index (WPI) ≥ 7 and symptom severity (SS) scale score ≥ 5, or WPI 3 to 6 and SS scale score ≥ 9,
    b. Pain in at least 11 of 18 specific tender point sites,
    c. Symptoms have been present at a similar level for at least 3 months, and
    d. The subject does not have a disorder that would otherwise explain the pain

6. ADPS of ≥ 4 on the 11-point numeric rating scale (NRS) over the 7 days prior to randomization (based on completion of at least 4 daily pain assessments during the 7-day baseline period prior to randomization)
7. Women of child bearing potential (WOCBP) must be using adequate methods of contraception (as detailed in Section 4.1.3) to avoid pregnancy during the study and for 4 weeks after study completion.

4.1.2. Exclusion Criteria

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

1. Need for ongoing use of concomitant chronic pain medications or any new non-pharmacological pain management techniques that may confound assessments of efficacy and/or safety, including neurolytic treatments (destruction of nerves by chemicals, heat, cold) or surgery, intrathecal pumps, spinal cord stimulators or psychological support within the previous year. Also excluded: topical capsaicin within 6 months; or systemic corticosteroids within 3 months of baseline period.
2. Unable to undergo pre-study washout of prohibited concomitant medications
3. Subjects with recent history (ie, within 1 year prior to screening) of alcohol abuse or illicit drug use (cocaine, heroin, marijuana [including medical, prescribed], etc.)
4. Use of any selective serotonin reuptake inhibitor (SSRI), unless the subject has been on a stable dose for ≥ 90 days prior to screening and is not anticipated to need any dose adjustment during the course of the study
5. Subjects with severe or uncontrolled depression that, in the judgment of the Investigator, makes the subject inappropriate for entry into the study
6. Significant neurological or psychiatric disorder unrelated to neuropathic pain
7. Other severe pain (eg, sciatica, rheumatoid arthritis) that might impair the assessment of neuropathic pain
8. CrCl ≥ 60 mL/min estimated from serum creatinine by the central laboratory using the Cockcroft-Gault equation.
9. Subjects who are on hemodialysis or who require hemodialysis before the follow-up assessment; acute renal failure; history of kidney transplant
10. Any history of a malignancy other than basal cell carcinoma within the past 5 years
11. Clinically significant unstable neurologic, ophthalmologic, hepatobiliary, respiratory, or hematologic illness or unstable cardiovascular disease (eg, severe hypotension, uncontrolled cardiac arrhythmia, or myocardial infarction) within 12 months prior to screening
12. Pregnancy or breast feeding or intent to become pregnant during the study period

13. Known hypersensitivity to $\alpha_2\delta$ ligands or other components of the study medications. Note: Prior exposure to DS-5565 is allowed, as long as hypersensitivity to DS-5565 was not observed.
14. Clinically significant ECG abnormalities at the Screening Visit
15. Subjects who are at risk of suicide, as defined by their responses to the C-SSRS or in the opinion of the Investigator. Note: Subjects answering "yes" to any of the C-SSRS questions must be excluded. Such subjects should be referred immediately to a mental health professional for appropriate evaluation.
16. Subjects with current severe or uncontrolled major depressive disorder or anxiety disorders as assessed by the Mini-international Neuropsychiatric Interview (MINI) interview (Version 6.0) at screening, or who answer "yes" to the suicidality question (current or past) on the Major Depressive Episode Module (Module A) or who answer "yes" to any question in the Suicidality Module (Module B) are excluded. Subject with mild to moderate major depression or anxiety disorders are permitted to enroll provided that the investigator assesses the subject as clinically stable and appropriate for entry into the study.
17. Subjects who are unlikely to comply with the protocol (eg, uncooperative attitude, inability to return for subsequent visits, and/or otherwise considered by the Investigator to be unlikely to complete the study)
18. Subject is currently enrolled in, or it has been fewer than 30 days since ending, another investigational device or drug study or is receiving another investigational agent.
19. Subjects who are employees or immediate family of employees of the study site, Sponsor, or contract research organization (CRO)
20. Screening laboratory values outside the limits listed in the table below:

Hematology	Hemoglobin	< 8 g/dL
	Platelet count	< 100,000/mm^3
	Absolute neutrophil count	< 1,500/mm^3
Blood chemistry	AST	> 2.0 × ULN
	ALT	> 2.0 × ULN
	Alkaline phosphatase	> 1.5 × ULN
	Total bilirubin	> 1.2 × ULN[a]
	Creatine kinase	> 3.0 × ULN
	Calculated CrCl	≥ 60 mL/min

[a] If a subject has total bilirubin > ULN, unconjugated and conjugated bilirubin fractions should be analyzed and only subjects documented to have Gilbert's syndrome may be enrolled.
Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, CrCl = creatinine clearance (determined by the central laboratory using the Cockcroft-Gault equation), ULN = upper limit of normal Women of Child Bearing Potential

4.1.3. Women of Child Bearing Potential

For the purposes of this study, all female participants will be considered as WOCBP unless they have undergone surgical sterilization (with documented hysterectomy, bilateral salpingectomy and bilateral oöphorectomy) or are postmenopausal and have a documented serum follicle stimulating hormone level > 35 mIU/mL (with or without hormone replacement therapy) and no menses within the previous 12 months.

WOCBP are permitted in the study but must consent to avoid becoming pregnant by using approved contraception methods throughout the study and for up to 4 weeks after completion, as described below.

Study-acceptable methods of birth control are double-barrier methods, which include a combination of any 2 of the following: systemic contraceptives, diaphragm, condom, any intrauterine device, partner's vasectomy, or sponge with spermicide. Spermicide can be used in combination with any of the other methods listed.

WOCBP must have a negative pregnancy test at all clinic visits.

Daiichi Sankyo must be notified of any study subject who becomes pregnant while participating in this clinical study, as described in Section 9.6.

4.2. Removal of Subjects From Therapy

Data from all randomized 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.

NOTE: In this study, the C-SSRS will be administered at all clinic visits. Based on the C-SSRS and investigator judgment, if a subject is identified as being at risk for suicide, appropriate safety measures should be implemented (see Section 3.1.5.2).

The MINI and C-SSRS are to be administered at any time during the study (including unscheduled visits) based on investigator's discretion (see Section 3.1.5.2).

4.2.1. Reasons for Withdrawal/Early Discontinuation

Any subject who discontinues from the study treatment for any reason will have their reason for study treatment discontinuation recorded on the eCRF using the following criteria.

For subjects withdrawn prior to randomization but after signing informed consent:

- Did not satisfy all inclusion/exclusion criteria
- Adverse event

- Lost to follow-up
- Withdrawal by subject (indicate reason)
- Physician decision
- Study terminated by Sponsor

For subjects discontinued or withdrawn after randomization but before completing the treatment period:

- Adverse event
- Death
- Lack of perceived efficacy by subject or investigator
- CrCl < 15 mL/min
- Lost to follow-up
- Protocol violation
- Study terminated by Sponsor
- Withdrawal by subject (indicate reason)
- Other (indicate reason)

A subject may be withdrawn due to non-compliance with any aspect of the protocol, as determined by the Investigator and/or the Sponsor's medical monitor or designee. Subjects who miss > 7 days of consecutive doses of study medication will be withdrawn from the study and early termination study procedures performed.

If the subject is withdrawn due to an adverse event, the Investigator will follow the subject until the adverse event has resolved or stabilized.

All subjects who are withdrawn from the study should complete protocol specified withdrawal procedures (Section 4.2.2).

4.2.2. Withdrawal Procedures

If a subject withdraws (or is withdrawn) from the study, the Investigator should complete and report all observations as thoroughly as possible up to the date of withdrawal, including the date of last treatment and the reason for withdrawal. Reasons recorded under "protocol violation" may include failure to comply with protocol requirements or study procedures, pregnancy, etc.

If the 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 all end-of-treatment/early termination procedures as soon as possible after early withdrawal. All subjects who are withdrawn from the study should return for post-treatment follow-up visits.

4.2.3. Subject Replacement

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

4.2.4. Subject Re-screening Procedures

Re-screening of subjects is not permitted except with permission from the sponsor.

5. TREATMENTS ADMINISTERED

5.1. Investigational Products

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

The investigational products for this study are:

- DS-5565 7.5 mg tablets
- Placebo tablets matching DS-5565 7.5 mg tablets

5.1.1. Method of Assigning Subjects to Treatments and Blinding

Randomization will be performed centrally using an IXRS. At the Screening Visit, the Investigator, or other site personnel under the direction of the Investigator, should contact or access the IXRS to register the subject, obtain the SID, and record the subject's initials, date of birth, sex, and initial screening date. Upon confirmation of a subject's eligibility at the Randomization Visit, the Investigator, or designee, will contact the IXRS to register the subject as randomized and obtain the identification number of the initial study medication blister pack ("wallet") to be dispensed to this subject. At each on-treatment visit, the Investigator, or designee, should contact the IXRS to record the subject's visit and status and obtain the correct wallet number to be dispensed at that visit. Study medication should only be dispensed in accordance with IXRS instructions and wallet number assignment. At the End-of-treatment/Early Termination Visits, the subject's visit and status should also be recorded using the IXRS.

The randomization schedule will be generated by an independent statistician at the CRO and reviewed and approved by a statistician at Daiichi Sankyo who is independent of all other aspects of study conduct. The randomization schedule will be maintained by the independent statistician at the CRO and will be kept strictly confidential. IXRS and Clinical Supply Operations personnel will have access to medication identification codes but will remain blinded to treatment. All other personnel involved with the conduct and the interpretation of the study, including the Investigators, investigational site personnel, and Daiichi Sankyo employees, will be blinded to the treatment until after the database lock.

Randomization will be stratified by CKD strata through the IXRS. Eligible subjects will be randomized in the ratio of 2:1 to receive 13 weeks of treatment with DS-5565 7.5 mg QD or placebo for CrCl 15-29 mL/min or with DS-5565 7.5 mg BID or placebo for CrCl 30-59 mL/min. In order to maintain the blind, the package will have one of the following morning and night dose schemes (BID: 2 active; QD: 1 active + placebo; Placebo: 2 placebo).

5.1.1.1. Emergency Unblinding for Safety Reasons

In the case of a rare emergency where, in the investigator's opinion, unblinding of the treatment is necessary in order to evaluate further course of action, the investigator

should access the IXRS and follow the instructions to initiate subject unblinding. The investigator may also contact the sponsor or designee's Medical Monitor for information related to DS5565's adverse effects in making the decision to unblind. (Contact information – please refer to the Study Operations Manual, which contains the key Medical Monitoring study personnel and their contact information.)

The investigator should promptly document and report to the sponsor any unblinding (eg, accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

In the event of unblinding, the subject will be informed about their treatment assignment (DS-5565 or placebo). If the subject is receiving DS-5565, the specific treatment group (7.5 mg QD or 7.5 mg BID) will not be revealed. Information about the treatment assignment must be restricted to designated study site staff/personnel that are providing immediate care to the subject. Any documentation of the treatment assignment must be maintained separately (i.e., a secured file). The information must not be included in the subject's source files to ensure the treatment assignment will remain blinded to the CRO monitor and other study personnel not involved with the subject's immediate care.

When an emergency unblinding has occurred, an automatic notification (via e-mail) will be sent to the Investigator and selected Daiichi Sankyo study personnel from the IXRS vendor. The notification will not contain any unblinding information. This will trigger the follow-up process to document the unblinding by completing the Emergency Unblinding by Investigator Form (to be provided by study personnel upon receipt of IXRS notification) and submit to Daiichi Sankyo Clinical Safety and Pharmacovigilance (CSPV); please refer to the form for completion instructions.

Once the study treatment has been unblinded, the study treatment should be discontinued, and the subject should leave the study treatment Phase. The subject will be seen for end-of-treatment assessments and follow-up, as defined in Section 6.5 and Section 6.6.

5.1.2. Method of Assessing Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. The identification number of all dispensed and returned study drug wallets should be recorded, along with the SID. The number of tablets used and remaining in each wallet should be documented at each on-treatment visit and the End-of-treatment/Early Termination Visit. If any tablets have been removed from the wallets (but not taken), these should be counted, documented, and retained.

Treatment compliance will be calculated by dividing the number of doses taken by the number of doses assigned for the appropriate visit interval (adjusted for any changes in the visit interval). Compliance for each visit interval is defined as taking at least 80% of the study drug dosage prescribed for that interval. If a subject is noncompliant, the subject will be counseled by study staff on the importance of taking the correct amount of study medication. As the primary analysis will follow the intent-to-treat principle, subjects should not be discontinued from the study for treatment noncompliance unless the subject meets the discontinuation criteria outlined in Section 4.2.1.

5.1.3. Labeling and Packaging

Double-blind study medication will be provided in labeled blister cards (wallets). The blister label will include all information required by federal and local regulations. Additional details on the investigational drug products, such as the expiration date, can be found in documentation accompanying drug shipment.

Code-break envelopes or scratch-off labels will not be used for unblinding in this study. Unblinding of individual subjects will be controlled using the IXRS (see Section 5.1.1).

5.1.4. Preparation

Double-blind study drug will be provided to sites as fully prepared blister cards (wallets). All wallets will have 1 tablet for the morning dose and 1 tablet for the bedtime dose for each day of dosing for both QD and BID, as well as placebo.

Study treatment can be taken irrespective of food intake. Wallets will be individually numbered; only the correctly numbered wallet(s) should be distributed to study subjects in accordance with IXRS instructions.

5.1.5. Storage

Drug supplies must be stored appropriately in a locked cabinet in a room with limited and controlled access under the recommended storage conditions. The recommended storage conditions are provided with the shipment of drug supplies (on the carton and wallets of Investigational material).

NOTE: If storage conditions go outside of the recommended storage conditions, the site must not dispense the affected supplies (affected supplies should be placed in quarantine per IXRS requirements). Proper notification processes must be followed immediately after receipt of IMP identified as having a temperature excursion.

5.1.6. Drug Accountability

When a drug shipment is received, the Investigator or designee will check the amount and condition of the drug, check for appropriate local language in the label, drug expiration date (if available), and register receipt in IXRS. The Investigator or designee shall report a problem with the shipment via IXRS as soon as possible, as well as follow the instructions on the Template® instruction form as they pertain to any temperature excursions.

A Drug Accountability Record will be provided to each site for documenting the use of the investigational product. The record must be kept current and should include the date and quantity of drug (number of wallets) received at each shipment, the SID (and initials) of each randomized subject for whom the investigational product was dispensed, the wallet numbers, date and quantities of investigational product dispensed at each visit, amount of remaining or returned product received at each subject visit (including the number of tablets inside or outside of returned wallets), and the initials of the dispenser.

At the end of the study, or as directed, all study treatment, including unused, partially used, or empty wallets, and any drug that may have been removed from the wallets (but

not taken), will be destroyed locally. If a site or country does not have a means for destruction, the material will be returned to the shipping depot, as instructed by the Sponsor. Investigational product will be destroyed or returned only after the study monitor has completed a final inventory to verify the quantity to be returned. The return and/or destruction of IP are to also be processed through the IXRS.

At the end of the study, a final investigational product reconciliation statement must be completed by the Investigator, or designee, and provided to the Sponsor. Unused drug supplies may be destroyed by the Investigator when approved in writing by the Sponsor and the Sponsor has received copies of the site's drug handling and disposition standard operating procedures (SOPs). The return of Investigational Product must be documented and the documentation included in the shipment as well as contained within the packing slip.

All investigational product inventory forms must be made available for inspection by the Sponsor's authorized representative (eg, CRO site monitor) and any authorized inspector from a regulatory agency. The Investigator is responsible for the accountability of all used and unused study supplies at the site.

5.2. Concomitant Medications

5.2.1. Prohibited Medications

Use of concomitant medications that may confound assessments of safety or efficacy is not permitted during the study. This is particularly important for analgesics and/or other medications or therapies that may be intended specifically as treatments for FM.

Subjects who are receiving medication for FM (or any prohibited medication listed in Table 5.1) will be required to undergo drug washout prior to the Baseline Period. The Investigator should comply with product labeling instructions for drug discontinuation (eg, tapering of opioids to avoid side effects related to dependence). Minimum washout requirements for specific classes of prohibited medications are provided in Table 5.1.

Subjects receiving treatment for FM should not begin washout of pain medication until they are determined to be potentially eligible for the study by the Investigator and contacted via telephone by the Investigator or designee.

Subjects should be instructed not to take any prohibited analgesic medicine, as listed on Table 5.1, during the Baseline Period, prior to Randomization, or during the subsequent treatment period. Use of prohibited medications may necessitate subject discontinuation from the study.

Table 5.1: Prohibited Medications and Treatments - During Baseline and Treatment Periods

Medication Class/Example Drugs	Minimum Washout Period Prior to Collection of Pre-Randomization Baseline Pain Assessments[a]
Anticonvulsants, including pregabalin and gabapentin	3 days
Opioids, including tramadol; tapentadol	7 days
COX-1 and -2 inhibitors	3 days
Benzodiazepines	7 days
Tricyclic antidepressants and SNRI (eg, duloxetine)	7 days
Other: Non-benzodiazepine hypnotics, such as zolpidem, skeletal muscle relaxants, topical capsaicin, chromium picolinate, local anesthetics, α-lipoic acid, evening primrose oil, fatty acid supplements, and memantine	3 days

[a] Investigators should also comply with product labeling recommendations for drug discontinuation.
COX-1 and -2 = cyclooxygenase type 1 and 2

Non-pharmacological therapies for neuropathic pain, such as acupuncture, laser therapy, spinal cord stimulation, electrical nerve stimulation, surgery, initiation of psychological support, or any other treatment designed to modulate the perception of pain, are also prohibited during the study.

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

5.2.2. Allowable Medications

Use of SSRIs (but not SNRIs) is allowed if the subject has been on a stable dose for ≥ 90 days prior to screening and is not anticipated to need adjustment during the study period.

Aspirin (up to 160 mg/day) for myocardial infarction and stroke prophylaxis is permitted.

Acetaminophen/paracetamol (up to 2 grams/day in divided doses at intervals of 4-6 hours) is the sole rescue medication. The use of all pain-related medications including acetaminophen/paracetamol must be documented as a concomitant medication. The reason or indication for its use should also be recorded as an adverse event in the eCRF. The subject should be instructed on risks associated with acetaminophen/paracetamol overdose.

Any other non-study medication taken by the subject during the course of the study should be recorded as a concomitant medication on the eCRF. The condition or indication should be recorded as an adverse event, as appropriate, and the dose, route of administration, start and end-of-treatment, and other relevant information (eg, reason for use) should be documented.

Birth control medications are permitted.

6. STUDY PROCEDURES

A study visit schedule in tabular format is provided in Section 17.

NOTE: The MINI and C-SSRS are to be administered at any time during the study (including unscheduled visits) based on investigator's discretion (Section 3.1.5.2).

6.1. Screening

If a subject does not have a creatinine clearance (CrCl) determination within 6 months prior to screening, a pre-screening determination should be done. If the CrCl level qualifies for the study, the subject may proceed to the full screening panel.

The screening period will last from the Screening Visit (Visit 1) up to the day of randomization (Visit 4). The screening period will include a Screening Visit (Visit 1), and a Baseline Visit (Visit 3), immediately followed by a 7-day baseline period (for assessment of baseline pain intensity using subject diaries). The duration of the Screening Period will be approximately 3 weeks, but no longer than 35 days.

Subjects receiving treatment for FM (or any prohibited medication listed in Section 5.2) will be required to undergo drug washout in accordance with instructions for treatment discontinuation on the respective product label (see Table 5.1 for minimum washout requirements). However, subjects receiving treatment for FM will be requested not to begin washout of pain medication until they are determined to be potentially eligible for the study by the Investigator. Once potential eligibility is confirmed, the Investigator, or a person designated by the Investigator, will contact the subject by telephone to begin the specified Washout Period. The name of the prior FM medication and date of last administration will be recorded on the eCRF.

All subjects will be required to undergo a 1-week Baseline Period (pre-randomization), during which daily pain scores will be recorded in electronic diaries. Electronic diaries will be distributed to subjects at start of the Baseline Period. Subjects who are not receiving treatment for FM (or any prohibited medication listed in Section 5.2) at or prior to the Screening Visit can begin the 1-week Baseline Period as soon as they are notified by the Investigator (or site personnel) that they are potentially eligible for participation in the trial. Subjects who require drug washout will begin the 1-week Baseline Period after they have completed the specified Washout Period. Fasting is not required prior to the Screening or Randomization Visits.

6.1.1. Screening Visit (Visit 1; Week ≤ -4, Prior to Randomization)

The initial Screening Visit should occur no more than 35 days prior to the Randomization Visit. No fasting is required for the Screening Visit. At the Screening Visit (Visit 1), subjects will be screened for participation based on assessment of all noninvasive eligibility criteria listed in Section 4.1. If a subject is considered likely to satisfy eligibility criteria, the Investigator is responsible for obtaining written informed consent from the subject, after providing an adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific

screening procedures or any study drugs are administered. For additional information on informed consent, refer to Section 1.5.2.

The following activities and/or assessments will be performed at/during the Screening Visit:

- Obtain written informed consent prior to performing any of the formal screening procedures.
- Administer the C-SSRS (see Section 9.3.1)
- Administer the M.I.N.I. Version 6.0 interview.
- Record demographic information
- Obtain medical and surgical history, including date of onset of FM
- Record prior and concomitant medications
- Record vital signs (temperature, heart rate, supine and orthostatic blood pressure), body height, and body weight
- Perform physical examination
- Perform neurological assessment
- Perform a 12-lead ECG (Section 9.9)
- Collect blood and urine samples for evaluation of standard clinical laboratory safety tests (chemistry, hematology, and urinalysis)
- Collect a blood sample for a serum pregnancy test on all WOCBP subjects
- Assess all applicable inclusion and exclusion criteria
- For subjects who require washout of pain medication, determine appropriate duration of the Washout Period, taking into account any labeling requirements for tapering of medication dose, as well as the minimal washout requirements listed in Table 5.1; instruct subjects not to begin washout until notified by phone they have satisfied all eligibility requirements (eg, documenting satisfactory laboratory results)
- Provide instructions on prohibited medications.
- Assess for and record AEs
- Contact IXRS to register the subject and obtain SID

6.1.2. Washout Telephone Contact (Visit 2, Week -3 to -1)

When the subject's potential eligibility is determined based on the results of the Visit 1 assessments, the site will contact the subject by telephone to schedule the Baseline Visit. If the subject is eligible and currently on a prohibited medication (see Table 5.1), the following activities and/or assessments will also be performed during this telephone contact (Visit 2):

- Assess for and record AEs

- Assess for and record prior and concomitant medication use
- Provide instructions on washout of current pain medication, including the duration of the Washout Period (per Table 5.1)

6.2. Baseline Visit (Visit 3, Week -1)

The Baseline Visit will occur after the subject has been determined to be potentially eligible (based on the results of the Visit 1 assessments), if the subject does not require a Washout Period or after the Washout Period, if applicable.

The following activities and/or assessments will be performed at/during the Baseline Visit:

- Assess for and record AEs
- Assess for and record concomitant medication use during the washout period (if applicable)
- Provide subjects with electronic daily diaries and instructions for recording baseline pain ratings every morning

6.3. Randomization Visit (Visit 4, Week 0)

The following activities and/or assessments will be performed at/during Randomization:

- Assess for and record AEs
- Record prior and concomitant medications
- Review subject's electronic daily diary data and ensure that diary data has been completed and transmitted properly.
- Administer the C-SSRS and evaluate for eligibility (see Section 9.3.1)
- Evaluate for continued eligibility. If the subject is found to be eligible based on the baseline ADPS and results of C-SSRS, proceed to perform the following procedures:
- Perform physical examination
- Perform neurological assessment
- Record vital signs (temperature, heart rate, supine and orthostatic blood pressure) and body weight
- Collect blood and urine samples for evaluation of standard clinical laboratory safety tests (chemistry, hematology, and urinalysis)
- Perform a urine pregnancy test for WOCBP. If positive, do not randomize. Collect a blood sample for serum pregnancy confirmation
- Contact IXRS to randomize subject and obtain study medication wallet number

- Dispense study medication wallet and review dosing instructions with the subject. The first dose of study medication is to be taken on the same day as the Randomization visit after completion of the study visit, at bedtime. Subjects are to be instructed to NOT take the "AM" dose in the medication wallet for Day 1

6.4. Treatment Period

The Treatment period begins with the first dose on the evening of the Randomization visit (Week 0) and concludes with the End of Treatment visit (Week 13, Visit 11), and therefore will be 13 weeks in duration. During the Treatment period, subjects will visit the clinic after 1 week of treatment (Week 1) and every 2 weeks thereafter (Weeks 3, 5, 7, 9, and 11).

- Fasting is not required prior to the visits.
- Subjects should be instructed to bring their electronic diaries and study medication wallets with them to each clinic visit.

Subjects should maintain their regular diary completion and dosing schedule (i.e., should complete their pain diaries upon awakening and take their morning dose before visiting the clinic) prior to the on-treatment visits, except as follows:

- Subjects should not take their morning dose before visiting the clinic on the morning of a PK sampling visit (Visits 5, 6, 8, and 10 [Weeks 1, 3, 7, and 11])

6.4.1. On-treatment Visits (Visit 5, Week 1; Visits 6-10, Weeks 3, 5, 7, 9, & 11)

The following activities and/or assessments will be performed at/during the on-treatment visits:

- Assess for and record AEs
- Record prior and concomitant medications
- Review daily diaries and ensure diary data has been transmitted properly
- Collect study medication wallets and review medication compliance
- Record vital signs (temperature, heart rate, supine and orthostatic blood pressure), and body weight
- Perform neurological assessment
- Collect blood and urine samples for evaluation of standard laboratory safety tests (chemistry, hematology, and urinalysis)
- PK blood sampling. These blood samples will be collected at the following visits:

  Visits 5, 6, 8, and 10 (Weeks 1, 3, 7, and 11)
- Complete the C-SSRS and evaluate for continued eligibility (see Section 9.3.1).
- Perform a urine pregnancy test on all WOCBP subjects
- Contact IXRS and obtain new study medication wallet number

- Dispense study drug and review dosing instructions. When subjects are assigned a new medication wallet, the first dose taken from the new medication wallet should be the "PM" dose on Day 1.

6.4.2. End-of-Treatment Visit (Visit 11, Week 13) or Early Termination

The following activities and/or assessments will be performed at the End-Of-Treatment visit (Week 13 ± 2 days) or at the Early Termination visit:

- Assess for and record AEs
- Record prior and concomitant medications
- Review daily diaries and ensure diary data has been transmitted properly
- Collect study medication wallets and review medication compliance
- Ask the subject to complete the PGIC
- Record vital signs (temperature, heart rate, supine and orthostatic blood pressure), and body weight
- Perform physical examination
- Perform neurological assessment
- Perform 12-lead ECG
- Collect blood and urine samples for evaluation of standard clinical laboratory safety tests (chemistry, hematology, and urinalysis)
- Complete the C-SSRS (see Section 9.3.1)
- Perform a urine pregnancy test on all WOCBP subjects; draw blood for serum pregnancy test
- Contact IXRS and update subject status

6.5. Post-treatment Follow-up

Post-treatment follow-up will be performed after the End of Treatment visit for those who complete the 13 week Treatment or after Early Termination visit for those terminated from the study early.

6.5.1. Telephone Contact Day 3 of Follow-up (Visit 12, Week 13.5)

The Day 3 Telephone Contact will occur 3 days (± 1 day) after the end of treatment or early termination visit as noted above. The following activities and/or assessments will be performed during the telephone contact:

- Assess for and record AEs
- Record prior and concomitant medications
- Administer PWC

6.5.2. Visit at Week 2 of Follow-up (Visit 13, Week 15)

The 2 Week Follow-up clinic visit will occur 2 weeks (± 3 days) after the end of treatment or early termination visit as noted above. The following activities and/or assessments will be performed during the clinic visit:

- Record vital signs (temperature, heart rate, supine and orthostatic blood pressure), and body weight
- Collect blood and urine samples for evaluation of standard clinical laboratory safety tests (chemistry, hematology, and urinalysis)
- Administer PWC
- Administer the C-SSRS (see Section 9.3.1)
- Perform urine pregnancy test on all WOCBP subjects
- Assess for and record AEs
- Record prior and concomitant medications

  Any abnormal findings (including abnormal laboratory values) observed at the last end of treatment visit should be rechecked at the Follow-up clinic visit.

6.5.3. Telephone contact at Week 4 of Follow-up (Visit 14, Week 17)

The 4 Week Follow-up telephone contact will occur 4 weeks (± 7 days) after the end of treatment or early termination visit as noted above. The following activities and/or assessments will be performed during the telephone contact:

- Assess for and record AEs
- Record prior and concomitant medications
- Administer PWC

6.6. Protocol Deviations

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

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

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

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

The Investigator should notify the IEC or IRB of deviations from the protocol in accordance with local procedures.

7. EFFICACY ASSESSMENTS

Efficacy assessments were secondary to the primary objective of safety and tolerability.

7.1. Primary Efficacy Assessments

Not applicable.

7.2. Secondary Efficacy Assessments

Secondary efficacy assessments for this study will include the ADPS and the PGIC.

7.2.1. Average Daily Pain Score

ADPS will be calculated by averaging up to 7 available pain scores. Pain scores will be recorded in a daily diary using an 11-point NRS ranging from 0 (no pain) to 10 (worst possible pain). Every morning upon awakening, prior to taking study medication, the subject will circle the number (0 to 10) that best describes the worst pain over the previous 24 hours.[6] The diary will be completed every morning upon awakening from the start of the baseline period (Day -6) through the morning following the last day of study drug administration. Baseline ADPS will be calculated as the average of the last 7 available pain ratings obtained during the Baseline Period, including the final rating on the morning prior to randomization (a minimum of 4 daily pain ratings will be required as an inclusion criterion). During the treatment period, weekly ADPS will be determined at the end of each week based on all available daily pain scores for the prior week.

7.2.2. Patient Global Impression of Change (PGIC)

Subjects will complete the PGIC using the study-specific tablet at the End-of-treatment visits (End of Treatment, Early Termination).

This standard instrument (refer to the Study Manual for a copy) is a well-validated outcome measure for pain treatment and shows close correlation with the 11-point pain intensity NRS in the setting of chronic pain.[7] The 7-point PGIC measures change in the subject's overall status using the following categorical scale: 1) very much improved, 2) much improved, 3) minimally improved, 4) no change, 5) minimally worse, 6) much worse, and 7) very much worse.

7.3. Exploratory Efficacy Variable(s)

Not applicable.

8. PHARMACOKINETIC/PHARMACODYNAMIC 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 5, 6, 8, and 10 (Weeks 1, 3, 7, and 11)

Blood (4 mL) will be collected into pre-chilled 2 mL Vacutainer™ K2 ethylenediamine tetraacetic acid tubes for the preparation of plasma and processed as described in the Laboratory Manual.

The time of the PK blood sample will be recorded in source documents and eCRFs. 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 date/time of the morning dose and the prior evening dose will be recorded in source documents and eCRF. The subject will be instructed 1 visit before the scheduled visit for PK sampling not to take study medication before coming to the site. An accurate reporting of times of dosing (on the previous day and on the morning of PK sampling) and PK sampling is important for population PK and exposure-response analyses.

PK analysis will only be conducted on subjects receiving DS-5565.

8.2. Pharmacodynamic (PD) Variable(s)

Not applicable.

8.3. Biomarker and Exploratory Variable(s)

Not applicable.

9. SAFETY ASSESSMENTS

9.1. Adverse Events

All clinical AEs occurring after the subject signs the ICF and up to 4 weeks after the last dose of study medication (i.e., follow-up period), whether observed by the Investigator or reported by the subject, will be recorded on the AE eCRF page. Medical conditions (including laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to informed consent will be recorded as part of medical history.

All clinical laboratory, vital sign, or ECG values should be appraised by the Investigator as to clinical significance. Isolated abnormal laboratory results, vital sign findings, or ECG findings should be reported as AEs if they are symptomatic, lead to study drug discontinuation, require corrective treatment, or are otherwise defined as an adverse event of special interest (AESI) [please refer to Section 9.7].

All SAEs are to be reported according to the procedures in Section 9.5. Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE. For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the ICF) procedure or treatment requiring hospitalization for pre-existing conditions, which do not worsen in severity, should not be reported as SAEs (see Section 9.4.2 for Definitions). For deaths, the underlying or immediate cause of death should always be reported as an SAE. In addition, any serious, untoward event that may occur subsequent to the reporting period that the Investigator assesses as related to study drug should also be reported and managed as an SAE.

At each visit, the Investigator will determine whether any adverse events have occurred by evaluating the subject. Adverse events may be directly observed, reported spontaneously by the subject, or by questioning the subject at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 9.4. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature. Investigator should follow subjects with AEs until the event has resolved or the condition has stabilized. In case of unresolved adverse events, including significant abnormal clinical laboratory values at the end of study assessment, these events will be followed up until resolution or until they become clinically not relevant.

9.2. Safety Assessments

The primary objective is the safety and tolerability of DS-5565.

9.3. Events of Special Interest

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

9.3.1. Suicidal Behavior and Ideation

An FDA-conducted pooled analysis of placebo-controlled clinical studies of antiepileptic drugs with varying mechanisms of actions and indications, including pregabalin and gabapentin, showed an increased risk of suicidal thoughts or behavior in patients receiving these drugs.

The C-SSRS and MINI are to be administered at any time during the study (including unscheduled visits) where the investigator/study coordinator/site staff recognizes or become aware of (and this includes if this awareness arises during unscheduled visits or non-face-to-face communications with the patient or his/her family):

- Any suggestion of mood disturbance and/or any awareness of a potential suicidal risk,
- Substantial changes in their psychosocial environment (ie, the death of or separation of close family/friend, sudden financial burden, worsening of medical condition, etc); in this case administration of the C-SSRS/MINI and consultation with a psychiatrist (onsite preferably) should be performed.

The C-SSRS will be administered at screening and at every clinical assessment thereafter. Based on the C-SSRS and investigator judgment, if a subject is identified as being at risk for suicide, appropriate safety measures should be implemented, including:

- A subject should be discontinued from the study, and immediately referred to a mental health professional for further evaluation, if a 'YES' response has been recorded for any question on the C-SSRS at any visit (current or past), unless the subject falls into the 'Possible Exception' category below.
  - Possible Exception (with regard to a 'YES' response(s) to C-SSRS Q1 and/or Q2 only):
  1. The benefit from continuation on the study medication significantly outweighs the risk of continuing the subject on study drug. Such cases need to be discussed with the sponsor medical director and should take into account the mental health professional evaluation AND
  2. The justification for continuing the subject in the study under these circumstances is to be appropriately documented per study procedure

Subjects should be discontinued from the clinical study and immediately referred to a mental health professional (preferably an onsite psychiatrist evaluation if possible) if subjects are assessed as having current severe or uncontrolled major depressive disorder or anxiety disorders by the MINI at any visit (current or past) and if any of the following conditions apply:

- The investigator determines that there is a suicidality risk, irrespective of any scales or
- Any "Yes" response to:
  - MINI questions
    - Module A (Major Depressive Disorder) question A3, G or
    - Any question on Module B (Suicidality) or
  - Relevant C-SSRS questions, with discontinuation criteria as outlined above.

9.3.2. Liver Enzyme Elevations/Liver Dysfunction

Increases in aminotransferases 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. 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 (i.e. including the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia) or an elevation of ALT or AST $\geq$ 3 x ULN (without clinical presentation suggestive of liver injury) at any visit should be monitored closely, according to the following:

- Repeat liver tests of at least all four of the usual serum measures (ALT, AST, alkaline phosphatase [ALP], and total bilirubin at least 2 times weekly [the first repeat should be within 48 to 72 hours of initial abnormality] until values have decreased to < 2 x ULN, then at least every 1 or 2 weeks until resolution or return to baseline). An additional 8.5 mL serum separating tube of blood will be collected at time of event and until values return to baseline. Samples will be stored for further analysis, as required.
- Review or obtain a detailed history of symptoms and prior or concurrent diseases
- Review or obtain a history of the use of concomitant drugs, including nonprescription medications, herbal and dietary supplements, alcohol, recreational drugs, and special diets
- Rule out alcoholic hepatitis, non-alcoholic steatohepatitis, hypoxic/ischemic hepatopathy, and biliary tract disease
- Obtain a history of exposure to environmental chemical agents
- Perform additional laboratory liver tests (eg, lactate dehydrogenase, ALP, gamma-glutamyl transpeptidase, prothrombin time), evaluations for potential viral etiologies (including hepatitis A, B, C, E; cytomegalovirus; and Epstein-

Barr virus) and autoimmune etiologies (anti-nuclear antibody, anti-smooth muscle antibody, anti-mitochondrial antibody)

Combined elevations of aminotransferases and bilirubin meeting the criteria of a potential Hy's Law case (ALT or AST ≥ 3 x ULN with simultaneous total bilirubin ≥ 2 x 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 9.5), with the Investigator's assessment of seriousness, causality, and a detailed narrative. (FDA's Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation; July 2009; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072278.pdf).[8] These events should be reported as soon as possible following the procedures outlined in Section 9.4 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 3.1.5.1.1.

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

9.4. Definitions

9.4.1. Adverse Event (AE)

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

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

9.4.2. Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

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

- Is an important medical event.

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

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

Note:

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

9.4.3. AE Severity

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

- Mild: Awareness of sign or symptom, but easily tolerated (i.e., 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 (i.e., interferes significantly with subject's usual function).

9.4.4. Causality Assessment

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

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

- 2 = Not Related:
  - The AE does not follow a reasonable sequence from study product administration, or can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

9.4.5. Action Taken Regarding the Study Product

- 1 = Dose Not Changed: No change in study drug dosage was made.
- 2 = Drug Withdrawn: The study product was permanently stopped.
- 3 = Drug Interrupted: The study product was temporarily stopped.

9.4.6. Adverse Event Outcome

- 1 = Recovered/Resolved
  - The subject fully recovered from the adverse event with no residual effect observed.
- 2 = Recovered/Resolved with Sequelae
  - The residual effects of the adverse event are still present and observable.
  - Include sequelae/residual effects.
- 3 = Not Recovered/Not Resolved
  - The AE itself is still present and observable.
- 4 = Fatal

9.4.7. Other Action Taken for Event

- 1 = None.
  - No treatment was required.
- 2 = Medication required.
  - Prescription and/or OTC medication was required to treat the AE.
- 3 = Other.

9.5. Serious Adverse Event Reporting Procedure For Investigators

All AEs, SAEs, and AESIs will be reported in the eCRF.

The following types of events should be reported in the eCRF within 24 hours of awareness:

- SAEs (see Section 9.4.2 for definition)

- Hepatic events meeting combination abnormalities (eg, ALT or AST ≥ 3 x ULN with simultaneous total bilirubin ≥ 2 x ULN) (potential Hy's Law case), both serious and non-serious
- Any event meeting the stopping rules for individual subjects (see Section 3.1.5.1).

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

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

In the event that the eCRF is unavailable, report SAEs by faxing the paper Serious Adverse Event Report (SAVER) Form to the CRO using the provided fax cover sheet and the appropriate fax number provided for your country. Once the eCRF becomes available, please enter SAEs reported on the SAVER Form into the eCRF as soon as possible. Please refer to the eCRF Completion Guide for additional instructions.

Please call the local SAE Hotline or your study monitor for any questions on SAE reporting.

9.5.1. Notifying Regulatory Authorities, Investigators, and IRB/EC

Daiichi Sankyo and/or CRO will inform Investigators, IRBs (Institutional Review Board)/ECs (Ethics Committees), and regulatory authorities of any Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring in other study centers or other Daiichi Sankyo studies of the investigational product, as appropriate per local reporting requirements.

In the US, upon receipt of the Sponsor's notification of SUSARs that occurred with the investigational product, unless delegated to the Sponsor, it is the Investigator's responsibility to inform the IRB per Sponsor's instruction.

In the European Economic Area states, it is the Sponsor's responsibility to report SUSARs to all ECs.

9.6. Exposure In Utero During Clinical Studies

Daiichi Sankyo must be notified of any subject who becomes pregnant while receiving or within 4 weeks of discontinuing the investigational product.

Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug

safety and public health concerns. It is the responsibility of the Investigator, or designee, to report any pregnancy in a female subject using the Exposure In Utero (EIU) Reporting form. Please contact your study monitor to receive the EIU Reporting Form upon learning of a pregnancy. The Investigator should make every effort to follow the subject until completion of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., post-partum complications, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the Investigator should follow the procedures for reporting SAEs outlined in Section 9.5.

9.7. Clinical Laboratory Evaluations

Blood and urine samples for clinical laboratory evaluations will be shipped to a central laboratory for analysis. Results of all clinical laboratory tests will be reported in the subject's eCRF or merged electronically with the clinical database.

9.7.1. Hematology

A single 4 mL EDTA tube of blood will be drawn for the hematology assessments listed in Table 9.1. These will be measured from samples obtained at the visits indicated at the Schedule of Events (Section 17).

Table 9.1: Hematology Analytes

Hemoglobin
Hematocrit
Red blood cell (RBC) count (with indices)
Reticulocyte count
White blood cell (WBC) count (with differential)
Platelet count

9.7.2. Blood Chemistry

An 8.5 mL serum separating tube of blood will be drawn for the blood chemistry assessments listed in Table 9.2. These will be measured from samples obtained at the visits indicated at the Schedule of Events (Section 17).

Table 9.2: Blood Chemistry Analytes

Sodium	Lactate Dehydrogenase
Potassium	Creatinine
Magnesium	Blood urea nitrogen
Bicarbonate	Total protein
Calcium	Albumin
Inorganic phosphorus	Uric acid
AST	Creatine kinase
ALT	Total cholesterol
ALP	Triglycerides
Total bilirubin	

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase;

9.7.2.1. Estimation of Creatinine Clearance

Creatinine clearance will be estimated from serum creatinine by the central laboratory using the Cockcroft-Gault equation.

9.7.3. Urinalysis

Standard urinalysis (Table 9.3), including a microscopic examination, will be conducted for all subjects at the visits indicated at the Schedule of Events (Section 17).

Table 9.3: Urinalysis Determinations

Specific gravity	Blood
pH	RBC
Protein	WBC
Glucose	Bilirubin
Ketones	Urobilinogen

RBC: red blood cell; WBC: white blood cell.

For samples with findings on macroscopic analysis, microscopic examination for RBCs, WBCs, bacteria, and casts should be performed.

9.7.4. Pregnancy Testing

Serum pregnancy testing will be performed for all WOCBP women, at the Screening and End-of-Treatment Visits. Urine pregnancy tests must be confirmed as negative before randomization and dispensing of study medication. If a urine test is positive, a blood sample will be drawn for serum confirmation.

9.8. Vital Signs

Vital signs will be recorded at all clinic visits (except the Baseline Visit) and will include temperature, heart rate, and supine and orthostatic blood pressure.

For measurement of supine blood pressure, subjects should be in a supine or semi-recumbent position for a minimum of 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 sphygmomanometer or automatic inflatable cuff monitor; the blood pressure cuff should be kept in place between supine and orthostatic blood pressure measurements.

Blood pressure should be measured using the same arm and measuring device throughout the study. At the Screening Visit (Visit 1) only, a blood pressure reading should be taken in both arms (unless there is a medical reason not to use a particular arm). The arm with the higher systolic reading should then be used throughout the rest of the study.

Blood pressure should be recorded to the nearest 2 mmHg mark on the manometer or to the nearest whole number on an automatic device.

9.9. Electrocardiograms

A 12-lead ECG will be conducted at the Screening Visit and at the End-of-treatment Visit. ECG recordings should be assessed as normal or abnormal, and any abnormal findings should be assessed as not clinically significant or significant. Clinically significant abnormal findings should be reported as medical history (if pre-existent or as AEs). Refer to Section 9.1 for general guidance on when to report abnormal findings as AEs.

9.10. Physical Findings

9.10.1. Body Height and Weight

Measurement of height will be performed at Screening Visit, with the subject in a standing position and with shoes removed. The subject's knees should be straightened, head held erect, with eyes forward.

Subjects should be weighed on the same scale when possible.

9.10.2. Physical Examinations

A full physical examination, with the exception of pelvis, breast, and rectum in women and the genitourinary system and prostate in men, will be performed at the Screening Visit and End-of-treatment Visit.

The full physical 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.

For a given subject, physical examinations should be performed by the same examiner when possible.

9.10.3. Neurological Examinations

A neurological examination will be performed at the indicated visits in the Schedule of Events (Section 17).

The neurological examination will include the following: Cranial nerve examination (sense of smell (I), visual fields and acuity (II), eye movements (III, IV, VI) and pupils (III, sympathetic and parasympathetic), sensory function of face (V), strength of facial (VII) and shoulder girdle muscles (XI), hearing (VII, VIII), taste (VII, IX, X), pharyngeal movement and reflex (IX, X), tongue movements (XII). Motor system examination includes muscle strength (0 to 5 rating; grip strength, elbow flexion, knee flexion, ankle dorsiflexion), muscle tone and signs of rigidity. Deep tendon reflexes (0 to 4 rating scale; biceps, brachioradialis, knee jerk, ankle jerk, plantar flexion [i.e., Babinski sign]), Sensory system testing by provoking sensations of fine touch, pain and temperature. Cerebellar testing (great toe and index finger, then proximal assessments; level of abnormality recorded), and gait/station (observation of regular walking, heel-to-toe [tandem] walking, each assessed as normal or abnormal).

For a given subject, neurological examinations should be performed by the same examiner when possible.

9.11. Other Safety Assessments

9.11.1. Columbia Suicide Severity Rating Scale

The C-SSRS will be administered by the Investigator or a qualified designee trained in its administration using the study-specific tablet at all the indicated visits in the Schedule of Events (Section 17).

The C-SSRS is a standardized instrument that was developed to assess the severity of and monitor changes in suicidal ideation and behavior.[9] Four constructs are measured. The first is severity of ideation, rated on a 5-point ordinal scale. The second is intensity of ideation, which comprises 5 items (frequency, duration, controllability, deterrents, and reason for ideation); each rated on a 5-point ordinal scale. The third is behavior, rated on a nominal scale that includes actual, aborted, and interrupted attempts; preparatory behavior; and non-suicidal self-injurious behavior. The fourth is lethality, which assesses actual attempts; actual lethality is rated on a 6-point ordinal scale, and if actual lethality is zero, potential lethality of attempts is rated on a 3-point ordinal scale.

9.11.2. Physician Withdrawal Checklist

The PWC will be administered by the Investigator or designee using the study-specific tablet at the Follow-up Visits 12, 13 and 14. At Follow-up Visits 12 and 14, the PWC will be administered by telephone.

Although developed specifically to measure symptoms of benzodiazepine withdrawal,[10] the PWC also has been used in studies of pregabalin.[11,12,13] The PWC rates 20 common

symptoms of withdrawal. The symptoms measured are based on those that are potentially related to benzodiazepine withdrawal: somatic, mood, cognitive, fatigue, and gastrointestinal.

Each of the 20 individual items on the PWC is rated as not present, mild, moderate, or severe. Individual items rated as mild, moderate or severe should not be handled as individual TEAEs. Rather, for any subject with at least 1 individual item rated as mild, moderate, or severe, the Investigator should report "withdrawal" as a TEAE.

In addition, the Investigator should be particularly attentive to any potential TEAEs that suggest opiate withdrawal at the Follow-up visits.

10. OTHER ASSESSMENTS

Not applicable.

11. STATISTICAL METHODS

11.1. Analysis Sets

The following analysis sets will be used to summarize the data from this study:

- The Randomized Analysis Set will include all subjects who signed the ICF and were randomized into the study.
- The Safety Analysis Set will include all subjects who received at least 1 dose of study medication.
- The modified Intent-to-treat (mITT) analysis set will include all randomized subjects who received at least 1 dose of study medication.
- The Per-Protocol Analysis Set will include all subjects who were randomized and received at least one dose of study medication, and who were sufficiently compliant with the protocol according to pre-specified criteria, which will be finalized prior to database unblinding.
- The PK Analysis Set will include all subjects who received at least one dose of DS-5565 and had at least one PK concentration measured.

11.2. General Statistical Considerations

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

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.

For variables expressed as a percentage, the denominators for the calculation of percentage will be the number of subjects who had that variable assessed.

A detailed SAP 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.

11.3. Study Population Data

Demographic characteristics will be summarized for the Randomized Analysis Set according to treatment assignment. Continuous demographic variables (age [calculated from date of birth to the date of first dose], weight, height, and body mass index) for all randomized subjects will be summarized with descriptive statistics. Categorical demographic variables (sex, race, ethnicity, and age group [eg, non-elderly, elderly, very elderly]) will be summarized with frequency counts and corresponding percentages.

Subject disposition will be summarized as the number of subjects screened, the number randomized, and the number and percentage of those who completed treatment or withdrew (with the latter summarized by reason for withdrawal).

Prior and concomitant medications will be summarized by number and percentage of subjects for each World Health Organization (WHO)-Drug preferred base name and Anatomical Therapeutic Chemical category.

11.4. Efficacy Analyses

11.4.1. Primary Efficacy Analyses

Not applicable.

11.4.2. Secondary Efficacy Analyses

For ADPS, change from baseline measured at randomization to Week 13/ET will be summarized by treatment and compared numerically between treatment groups.

For PGIC at Week 13/ET, the proportions of subjects who are "minimally improved or better" (i.e., score ≤ 3) and of subjects who are "much improved or better" (ie, score ≤ 2) will be summarized and compared numerically between treatment groups.

For each efficacy endpoint, between treatments group differences will be summarized within each CKD stratum by calculating 95% confidence intervals.

11.4.3. Exploratory Efficacy Analyses

Not applicable.

11.5. Pharmacokinetic Analyses

PK analyses, summaries, and listings will be generated by dose group using the PK analysis set. Descriptive statistics for plasma concentrations of DS-5565 (sample size, mean, SD, coefficient of variation, standard error of the mean, minimum, maximum, and median) will be calculated at each evaluation time-point.

A population PK model will be developed to quantify the potential impact of demographic covariates on the exposure to DS-5565. For this purpose, data from this study may be pooled with data from other DS-5565 studies and reported separately from the clinical study report.

11.6. Safety Analyses

For safety endpoints, the data from AE assessments, clinical laboratory assessments, physical and neurologic examinations, 12-lead ECGs, vital signs (including weight) assessments, C-SSRS, and PWC evaluation will make up the safety analyses. The Safety Analysis Set will be used for all safety analyses.

The primary objective is the safety and tolerability of DS-5565. Safety data will be summarized by treatment group. 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.

11.6.1. Adverse Event Analyses

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. A TEAE is defined as an AE that emerges during treatment (having been absent prior to treatment) or worsens relative to the pre-treatment state. The frequency of patients experiencing a specific TEAE will be tabulated by treatment, system organ class, preferred term, seriousness (see Section 9.4.2), worst severity (see Section 9.4.3), and relationship to study drug (see Section 9.4.4). Treatment-emergent AEs of special interest (defined in the SAP) will be summarized separately. In the by-subject analysis, a subject having the same event more than once will be counted only once. Listings of deaths, SAEs, and AEs leading to treatment discontinuation of a subject will be presented.

11.6.2. Clinical Laboratory Analyses

Hematology, serum chemistry, and urinalysis parameters evaluated at each planned assessment, and changes from baseline at each planned post-baseline assessment, will be summarized by treatment group. Shift tables (in categories of low, normal, and high, when appropriate) will be provided by treatment group. Subjects with abnormal values will be identified in the data listings.

11.6.3. Vital Sign Analyses

Vital sign findings at each planned assessment, and changes from baseline at each planned post-baseline assessment, will be summarized by treatment group.

11.6.4. Electrocardiogram Analyses

ECG data will be listed and summarized by treatment group and visit. Shift tables for ECG results (normal or abnormal) will be presented by treatment group to show changes from baseline (normal or abnormal) to end-of-treatment (normal or abnormal).

11.6.5. Physical Examination Analyses

Clinically significant abnormal physical examination findings will be reported as AEs. Data from physical examinations will be listed and summarized by treatment group and visit.

11.6.6. Neurological Examinations

Data from neurological examinations will be listed and summarized by treatment group and visit.

11.6.7. Columbia-Suicide Severity Rating Scale

C-SSRS data will be listed and summarized by treatment group and visit.

11.6.8. Physician Withdrawal Checklist

PWC data will be listed and summarized by treatment group and visit.

11.7. Other Analyses

Not applicable.

11.8. Interim 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 the DS-5565 Phase 3 program. 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 until further notice, with recommendations for further action to address specific issues and appropriately managing active study subjects
- Terminate the study 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 Sponsor (Head of CSPV) will be notified of the DSMB decision by the DSMB chairman within 3 days 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 from the DS-5565 Phase 3 program. 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 clinical laboratory reports.

11.11. Sample Size Determination

Approximately 60 subjects will be randomized. Assuming a 25% dropout rate, approximately 45 subjects will complete the double-blind treatment period. This sample size is thought to be sufficient to address the objectives of this clinical trial. All attempts will be made to enroll a reasonable distribution of patients with moderate to severe renal insufficiency in this study.

12. DATA INTEGRITY AND QUALITY ASSURANCE

The Investigator/investigational site will permit study-related monitoring, audits, IRB/IEC 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 Sponsor or designee's 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 site(s) at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH GCP and local regulations on the conduct of clinical research. The monitor is responsible for inspecting the CRFs and ensuring completeness of the study essential documents. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the CRFs.

The monitor will communicate deviations from the protocol, SOPs, 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 Sponsor. Inspection of site facilities (eg, pharmacy, drug storage areas, laboratories, etc.) and review of study-related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

12.2. Data Collection

All relevant observations and data related to the study, as per the study protocol, will be recorded on eCRF pages. A representative of Daiichi Sankyo or their designee will provide instruction for completing the eCRF. Adequate and accurate case records should be maintained, including the evaluation of inclusion and exclusion criteria, medical history, physical examinations, clinical assessments, a record of clinical safety laboratory sample collection, drug administration, AEs, and final evaluation.

The eCRFs must be completed for each subject who signs the ICF and undergoes screening procedures. For subjects who are screened but not randomized, minimal data will be recorded on the eCRF, including demography, subject status, and AEs. All study-related data for these subjects will be maintained in the medical records at the site.

The eCRF data entry shall be completed on the day of the visit or as soon as possible thereafter. The Investigator must electronically sign and date the eCRF. The signature shall indicate that the Investigator has reviewed the data and data queries recorded on eCRFs and the site notifications, and agrees with the content. After the completion of the study, eCRFs including audit trail will be returned to Daiichi Sankyo and stored in the archives.

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 sites, a Clinical Data Management review will be performed on subject data according to specifications given to the Sponsor or designee. 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, the data will be reviewed for adherence to the protocol and GCP. For eCRFs, the data will be electronically vetted by programmed data rules within the application. Queries generated by rules and raised by reviewers will be generated within the electronic data capture (EDC) application and also resolved within the EDC application.

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

Serious adverse events in the clinical database will be reconciled with the safety database.

All medical history (except pre-printed terms) and AEs will be coded using MedDRA. All prior and concomitant medications will be coded using WHO Drug Dictionary.

12.4. Study Documentation and Storage

The Investigator will maintain a Signature List of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Signature List.

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

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

- Subject files containing completed CRFs, informed consents, and supporting copies of source documentation (if kept).
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of relevant essential documents required prior to

commencing a clinical study, and all correspondence to and from the IEC/IRB and the Sponsor.

- Records related to the Investigational Product(s) including acknowledgment of receipt at site, accountability records and final reconciliation and applicable correspondence.

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

All essential documentation will be retained by the institution until told 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.

All Investigators and site personnel must ensure subject confidentiality as outlined in Section 1.5.1.

12.5. Record Keeping

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

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 the Sponsor or designee. 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

[redacted]

15. STUDY ADMINISTRATIVE INFORMATION

15.1. Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be communicated to the Investigator by the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB/EC and regulatory authorities, where relevant, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB/EC within five working days. The Sponsor will assure the timely submission of amendments to regulatory authorities.

15.2. Address List

A list of key study personnel (including personnel at the Sponsor, CRO, laboratories, and other vendors) and their contact information (address, telephone, fax, email) will be kept on file and updated in the Study Operations Manual.

16. REFERENCES

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17. SCHEDULE OF EVENTS

Table 17.1: Schedule of Events

Study Period	Screening/Baseline[a]			Randomization	Treatment		End of Tx or ET	3-Day FU	2 Week Follow-up	4 Week Follow-up
Visit	1	2	3	4	5	6-10	11	12	13	14
Week	≤ -4	-3 to-1	-1	0	1	biweekly	13	13.5	15	17
Visit Window (days)	--			--	±2	±2	±2	±1	±3	±7
Telephone Contact		X						X		X
Study informed consent	X									
Inclusion/exclusion criteria	X			X						
Demographic information	X									
Medical/surgical history	X									
Dispense Daily eDiary			X							
Review daily diaries				X	X	X	X			
Physical examination	X			X			X			
Neurological assessment	X			X	X	X	X			
Vital signs	X			X	X	X	X		X	
12-lead electrocardiogram	X						X			
Clinical laboratory evaluations	X			X	X	X	X		X	
PWC[b]								X	X	X
C-SSRS	X			X	X	X	X		X	
M.I.N.I (Version 6.0)	X									
PK blood sampling					X[c]	X[c]				
Pregnancy test	X			X[d]	X[d]	X[d]	X		X[d]	
Adverse event reporting	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X
Study drug dispensing				X	X	X				
Study drug compliance					X	X	X			
Contact IXRS	X			X	X	X	X			

PGIC							X			

[a] Screening period comprises an initial clinic visit (Visit 1), a telephone contact (Visit 2), and a clinic visit at the start of the Baseline Period (Visit 3) at which time subjects will be given an electronic daily diary for recording of pain scores at home.
[b] All subjects have PWC during follow-up. Subjects discontinued from study at or before Visit 11 (Week 13) will begin follow-up 3 days later with Visit 12 telephone contact.
[c] PK sampling at Weeks 1, 3, 7, and 11.
[d] Urine pregnancy tests for WOCBP at these visits; if positive, also serum test; urine and serum tests at screening, end of treatment or early termination.
Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale, ET = Early Termination, FU = follow-up, M.I.N.I = Mini International Neuropsychiatric Interview (Version 6.0), PGIC = Patient Global Impression of Change, PK = pharmacokinetic, PWC = Physician Withdrawal Checklist, Tx = treatment, WOCBP = women of childbearing potential; IXRS = Interactive Web/Voice/ Web Response System.