CLINICAL STUDY PROTOCOL

AN OPEN-LABEL EXTENSION STUDY OF DS-5565 FOR 52 WEEKS IN PAIN ASSOCIATED WITH FIBROMYALGIA

DS5565-A-E312

IND 118,304

EUDRACT NUMBER 2013-005164-26

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SPONSOR	**Daiichi Sankyo Pharma Development** **399 Thornall Street** **Edison, NJ 08837 United States**
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INVESTIGATOR AGREEMENT

AN OPEN-LABEL EXTENSION STUDY OF DS-5565 FOR 52 WEEKS IN PAIN ASSOCIATED WITH FIBROMYALGIA

Sponsor Approval:

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

[redacted] | [redacted]

Print Name | Signature

Senior Director, Clinical Development | 14 Mar 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

Title | Date (DD MMM YYYY)

PROTOCOL SYNOPSIS

IND/EudraCT Number:	118,304/2013-005164-26
Protocol Number:	DS5565-A-E312
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
Study Title:	An Open-label Extension Study of DS-5565 for 52 Weeks in Pain Associated with Fibromyalgia
Study Phase:	Phase 3
Indication Under Investigation:	Pain associated with fibromyalgia (FM)
Study Objectives:	The primary objective is to assess the long-term safety of DS-5565 in subjects with FM. The secondary objectives are: • To observe the effects of DS-5565 on average daily pain score (ADPS) and pain-associated sleep interference as assessed by average daily sleep interference score (ADSIS) (both recorded in a diary). Weekly ADPS is based on daily pain scores reported by the subject that best describes his or her worst pain over the previous 24 hours • To observe the effects of DS-5565 on Patient Global Impression of Change (PGIC) • To observe the effects of DS-5565 on depression and anxiety as assessed by the Hospital Anxiety and Depression Scale (HADS) • To observe the effects of DS-5565 on subject quality of life as assessed by the EuroQoL Instrument 5 Domains (EQ-5D) and the Short Form 36 (SF-36)
Study Design:	This is an open-label study of DS-5565 in subjects who either completed participation in a preceding Phase 3 study of DS-5565 in FM (i.e. DS5565-A-E309, DS5565-A-E310, or DS5565-A-E311) or are de novo subjects. Eligible

	subjects will be assigned to receive open-label DS-5565 for 52 weeks. All subjects will receive DS-5565 15 mg once daily (QD) for the first three weeks of the treatment period. After three weeks, subjects may be titrated to 15 mg twice daily (BID) based on protocol-specified criteria.
Study Duration:	For rollover subjects, the total study duration (for an individual subject's participation) will be approximately 56 weeks, including 52 weeks of open-label treatment and 4 weeks of post-treatment follow-up. De novo subjects will also have a screening/baseline period of up to 3 weeks and therefore a total duration of approximately 59 weeks.
Study Sites and Location:	This is a worldwide study which includes sites that conducted one of the preceding studies of DS-5565 in FM (DS5565-A-E309, DS5565-A-E310, or DS5565-A-E311) and sites that did not conduct one of the preceding DS5565 studies as listed above.
Planned Sample Size:	Subjects who complete the double-blind studies are eligible to rollover to this open-label extension study. Although it's unknown how many subjects will complete the double-blind studies, the number is anticipated to be between 2100 and 2500. In addition subjects who did not participate in a preceding double-blind study (referred to as de novo subjects) may be enrolled. Overall, the goal of the open-label extension study is to collect long-term safety data on approximately 500 subjects exposed to DS-5565 for at least 52 weeks. During the conduct of the open-label study, subject withdrawal rates will be closely monitored. Entry into the open-label study will be stopped when the sponsor anticipates that the desired number of subjects completing 52 weeks can be achieved.
Subject Eligibility Criteria:	<u>Inclusion Criteria:</u> *Subjects who completed a Phase 3 DS-5565 study (DS5565-A-E309, DS5565-A-E310, or DS5565-A-E311)* 1. Able to give written informed consent 2. Completed participation (i.e. completed the End-of-Tapering visit) in a preceding study of DS-5565 in FM (DS5565-A-E309, DS5565-A-E310, or DS5565-A-E311) 3. Women of child-bearing potential (WOCBP) must be using an adequate method of contraception (as

detailed in the body of the protocol) to avoid pregnancy during the study and for 4 weeks after study completion

4. The subject must not have experienced any significant safety issues during the preceding study that, in the investigator's judgment, would adversely impact the subject's well-being in the long-term extension

De Novo Subjects

5. Age ≥ 18 years
6. Able to give written informed consent
7. Able to complete subject-reported questionnaires per the investigator's judgment
8. At screening, subjects must meet the 1990 American College of Rheumatology (ACR) criteria for FM, i.e. widespread pain present for at least 3 months and pain in at least 11 of 18 specific tender point sites. In addition, the 2010 ACR criteria must be met:
   - Widespread pain index (WPI) ≥ 7 and symptom severity (SS) scale score ≥ 5, or WPI 3 to 6 and SS scale score ≥ 9
   - Symptoms have been present at a similar level for at least 3 months
   - The subject does not have a disorder that would otherwise explain the pain
9. ADPS of ≥ 4 on the 11-point numeric rating scale (NRS) over the past 7 days prior to first dose (based on completion of at least 4 daily pain diaries during the 7-day baseline period)
10. Subject must have documented evidence of a fundoscopic examination (with pupil dilation) or a scanning laser ophthalmoscopy examination within 12 months prior to screening or at screening
11. WOCBP must be using an adequate method of contraception (as detailed in the body of the protocol) to avoid pregnancy during the study and for 4 weeks after study completion

Exclusion Criteria:

All Subjects

1. Clinically significant unstable neurologic, psychiatric, ophthalmologic, hepatobiliary, respiratory, or hematologic illness or unstable cardiovascular disease (e.g. severe hypotension, uncontrolled cardiac arrhythmia, or myocardial infarction) or any other concurrent disease during the preceding study (for rollover subjects) or within 12 months prior to screening (for de novo subjects) that in the opinion of the investigator would interfere with study participation or assessment of safety and tolerability
2. Subjects who are at risk of suicide as defined by their responses to the Columbia-Suicide Severity Rating Scale (C-SSRS) or in the opinion of the investigator. Note: Subjects answering "yes" to any of the questions about active suicidal ideation/intent/behaviors occurring within the past 12 months must be excluded (C-SSRS Suicide Ideation section – Questions 3, 4, or 5; C-SSRS Suicidal Behavior section, any of the suicide behaviors questions). Such subjects should be referred immediately to a mental health professional for appropriate evaluation
3. Subjects who are unlikely to comply with the protocol (e.g. uncooperative attitude, inability to return for subsequent visits) and/or otherwise considered by the investigator to be unlikely to complete the study
4. Subjects with severe or uncontrolled depression that, in the judgment of the investigator, makes the subject inappropriate for entry into the study
5. Subjects with pain due to other conditions (e.g. diabetic peripheral neuropathic pain or post-herpetic neuralgia) that in the opinion of the investigator would confound assessment or self-evaluation of the pain associated with FM
6. Subjects with pain due to any widespread inflammatory musculoskeletal disorder (e.g., rheumatoid arthritis, lupus) or widespread rheumatic disease other than FM
7. Abuse or dependence of prescription medications, street drugs, or alcohol within the last 1 year
8. Any history of a malignancy other than basal cell

carcinoma within the past 5 years

9. A diagnosis of untreated sleep apnea or initiation of treatment for sleep apnea within the past 3 months
10. Known hypersensitivity to alpha$_2$-delta ($\alpha_2\delta$) ligands or other components of the study medications.
11. Pregnancy or breast-feeding, or intent to become pregnant during the study period
12. Abnormal investigative tests (i.e. ECGs) and laboratory values judged by the investigator to be clinically significant at the End-of-Treatment visit (Visit 11, Week 13) in the preceding study (for rollover subjects) or at screening (for de novo subjects), with particular focus on:
    - Abnormal renal function defined as calculated creatinine clearance (CrCl) < 60 mL/min determined by the central laboratory using the Cockcroft-Gault equation; blood urea nitrogen> 1.5 × upper limit of normal (ULN); serum creatinine > 1.6 mg/dL (> 141.4 µmol/L); or
    - Abnormal liver function defined as aspartate aminotransferase (AST) > 2.0 × ULN, alanine aminotransferase (ALT) > 2.0 × ULN; alkaline phosphatase > 1.5 × ULN; total bilirubin> 1.2 × ULN. If a subject has total bilirubin > 1.2 ULN, unconjugated and conjugated bilirubin fractions should be analyzed and only subjects documented to have Gilbert's syndrome may be enrolled; or
    - Creatine kinase > 3.0 × ULN;

For De Novo Subjects Only

13. Unable to undergo pre-study washout of prohibited concomitant medications (as listed in Section 5.2.1 of the protocol)
14. 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 are excluded, but mild to moderate major depression or anxiety disorders are permitted provided that the investigator assesses the patient as clinically stable and appropriate for entry into the study
15. Any diagnosis of lifetime bipolar disorder or

	psychotic disorder 16. Subject is currently enrolled in or has not yet completed at least 30 days since ending another investigational device or drug study or is receiving other investigational agents 17. Subject is an employee of the study center, an immediate family member* of an employee of the study center, or an employee of Daiichi Sankyo, INC Research, or any of the study vendors supporting this study. *(spouse, parent, child, or sibling, whether biological or legally adopted)
Dosage Form, Dose and Route of Administration:	Open-label study medication will be provided in blister cards ("wallets"). DS-5565 is supplied in the form of 15 mg tablets for oral administration. Doses of DS-5565 include 15 mg QD and 15 mg BID. Each subject will take (orally) 1 tablet either QD at bedtime or BID in the morning and at bedtime.
Study Endpoints:	The primary endpoint is long-term safety based on assessment of treatment-emergent adverse events (TEAEs), clinical laboratory evaluations, physical examinations, electrocardiograms (ECGs), the C-SSRS, and the Physician Withdrawal Checklist (PWC). The secondary endpoints are: • Changes from baseline to scheduled timepoint in ADPS and ADSIS • Proportion of subjects with improvement in overall status at Week 52 as assessed by PGIC • Changes from baseline to Week 52 in HADS depression and anxiety scores • Changes in EQ-5D and SF-36 parameters from baseline to Week 52
Statistical Analyses:	Efficacy and safety data will be summarized using descriptive statistics; any analyses will be exploratory and not formal.

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
$\alpha_2\delta$	alpha$_2$-delta
ADPS	average daily pain score
ADSIS	average daily sleep interference score
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BID	twice daily
CFR	Code of Federal Regulations
CrCl	creatinine clearance
C_{max}	maximum plasma concentration
CMV	cytomegalovirus
COX-2	cyclooxygenase type 2
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DPNP	diabetic peripheral neuropathic pain
DSMB	Data and Safety Monitoring Board
EBV	Epstein-Barr virus
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EIU	Exposure In Utero
EQ-5D	EuroQoL Instrument 5 Domains
FDA	Food and Drug Administration
FM	fibromyalgia
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Conference on Harmonisation

ABBREVIATION	DEFINITION
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IXRS	interactive voice/web response system
MCS	mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drug
PCS	physical component summary
PD	pharmacodynamic(s)
PGIC	Patient Global Impression of Change
PK	pharmacokinetic(s)
PWC	Physician Withdrawal Checklist
QD	once daily
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SAVER	Serious Adverse Event Report
SF-36	Short Form 36
SID	subject identification number
SOP	standard operating procedure
SNRI	serotonin-norepinephrine reuptake inhibitors
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse event reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization
WOCBP	Women of child-bearing potential

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Data Summary

1.1.1. Investigational Product(s)

1.1.1.1. Name

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

1.1.1.2. Description

DS-5565 is a potent and specific ligand of the alpha$_2$-delta ($\alpha_2\delta$) subunit of voltage-dependent Ca^{2+} channels and has been identified as the molecular target for the analgesic effects of pregabalin, currently marketed in the United States (US) for the management of fibromyalgia (FM), thus establishing an important therapeutic target for pain control.[1]

1.1.1.3. Intended Use Under Investigation

DS-5565 is being developed as treatment for pain associated with FM.

1.1.1.4. Nonclinical Studies

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.

1.1.1.5. Clinical Experience

Fourteen Phase 1 clinical pharmacology studies of DS-5565 and two Phase 2 studies of DS-5565 in subjects with DPNP have been completed. Data from these completed studies have characterized the clinical pharmacology and safety profile of DS-5565 and have provided proof-of-concept for DS-5565 as a treatment for chronic pain.

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

1.2. Study Rationale

DS-5565 is an oral analgesic drug being developed for chronic use in FM and other indications. This open-label extension study will provide important long-term safety data in subjects who will be dosed on DS-5565 for up to 1 year.

1.3. Risks and Benefits for Study Subjects

The results from nonclinical and clinical studies suggest that subjects treated with DS-5565 may experience improvement in pain associated with FM.

Anticipated risks of DS-5565 include the occurrence of adverse reactions related to central nervous system 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.

A detailed description of efficacy and 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 male and female subjects with an FM diagnosis, confirmed according to American College of Rheumatology 1990 and 2010 criteria based on the Widespread Pain Index and Symptom Severity Scale as well as assessment of tender points, who have completed participation in a previous Phase 3 study of DS-5565 in FM (DS5565-A-E309, DS5565-A-E310, or DS5565-A-E311). In addition subjects who did not participate in a preceding double-blind study (referred to as de novo subjects) may be enrolled. Full details regarding eligibility criteria are provided in Section 4.

For all subjects, the duration of open-label treatment (DS-5565 15 mg QD or DS-5565 15 mg twice daily [BID] [see Section 5.1.1]) will be 52 weeks.

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:

- European Commission Directive (2001/20/EC Apr 2001) and/or
- European Commission Directive (2005/28/EC Apr 2005) and/or
- FDA GCP Regulations: Code of Federal Regulations (CFR) Title 21, parts 11, 50, 54, 56 and 312 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 (eCRFs) 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 (e.g. 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 company, 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

For rollover subjects, the investigator must obtain the subject's consent before the start of the End-of-Tapering visit (Week 14, Visit 13) of one of the preceding studies (DS5565-A-E309, DS5565-A-E310, or DS5565-A-E311), because information from that End-of-Tapering visit will also be used in the current study. For de novo subjects, the subject's consent will be obtained at the Screening visit (Visit 1).

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 IEC or IRB prior to being provided to potential subjects.

The subject's written informed consent should be obtained prior to his/her participation in the study (for rollover subjects, before the start of the End-of-Tapering visit of one of the preceding studies), and should be documented in the subject's medical records, as required by 21 CFR Part 312.62. 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 eCRF.

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

Additional consent is required for all subjects in the US, in accordance with the Health Insurance Portability and Accountability Act (HIPAA).

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 (e.g. advertisements), information about payments and compensation available to the subjects, and documentation evidencing the investigator's qualifications should be submitted to the IEC or IRB for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

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

The investigator must submit and, where necessary, obtain approval from the IEC or IRB 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 IEC or IRB of deviations from the protocol or serious adverse events (SAEs) occurring at the site and other adverse event (AE) reports received from the sponsor or designee, in accordance with local procedures.

As required by local regulations, the sponsor's local Regulatory Affairs group or designee will ensure 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

The primary objective is to assess the long-term safety of DS-5565 in subjects with FM.

The secondary objectives are:

- To observe the effects of DS-5565 on average daily pain score (ADPS) and pain-associated average daily sleep interference score (ADSIS) (both recorded in a diary). Weekly ADPS is based on daily pain scores reported by the subject that best describes his or her worst pain over the previous 24 hours.
- To observe the effects of DS-5565 on Patient Global Impression of Change (PGIC)
- To observe the effects of DS-5565 on depression and anxiety as assessed by the Hospital Anxiety and Depression Scale (HADS)
- To observe the effects of DS-5565 on subject quality of life as assessed by the EuroQoL Instrument 5 Domains (EQ-5D) and the Short Form 36 (SF-36).

2.2. Study Hypothesis

The hypothesis of this long-term, open-label extension study is that DS-5565 will be generally well tolerated when administered for up to 1 year with no significant safety signals.

3. STUDY DESIGN

3.1. Overall Plan

3.1.1. Study Type

This is an open-label study of DS-5565 in subjects who either completed participation in a preceding Phase 3 study of DS-5565 in FM (i.e. DS5565-A-E309, DS5565-A-E310, or DS5565-A-E311) or are de novo subjects. For rollover subjects, enrollment procedures are structured to avoid a gap in treatment between the preceding study and this extension study (for rollover subjects). The Start-of-Treatment visit (Visit 4) for this extension study will occur on the same day as the End-of-Tapering visit (Visit 13) for the preceding studies. For de novo subjects, screening and baseline procedures will be performed at Visits 1 to 3. Eligible subjects will be assigned to receive open-label DS-5565 for 52 weeks. All subjects will receive DS-5565 15 mg once daily (QD) for the first three weeks of the treatment period. After three weeks, subjects may be titrated to 15 mg BID based on efficacy and safety criteria as detailed in Section 5.1.1.

3.1.2. Treatment Groups

In this study, subjects will initially be given open-label DS-5565 15 mg QD. After treatment at this dose for 3 weeks (Visit 6, Week 3), subjects may be titrated to 15 mg BID based on efficacy and safety criteria as detailed in Section 5.1.1.

3.1.3. Study Endpoints

The primary endpoint is long-term safety based on assessment of treatment-emergent adverse events (TEAEs), clinical laboratory evaluations, physical examinations, electrocardiograms (ECGs), the Columbia-Suicide Severity Rating Scale (C-SSRS), and the Physician Withdrawal Checklist (PWC).

The secondary endpoints are:

- Changes from baseline to scheduled timepoint in ADPS and ADSIS
- Proportion of subjects with improvement in overall status at Week 52 as assessed by PGIC
- Changes from baseline to Week 52 in HADS depression and anxiety scores
- Changes in EQ-5D and SF-36 parameters from baseline to Week 52

3.1.4. Duration of the Study

The total duration of the study from First Subject Screened to Last Subject Last Visit is estimated to be approximately 39 months.

3.1.5. Duration of Subject Participation

For rollover subjects, the total study duration (for an individual subject's participation) will be approximately 56 weeks, including 52 weeks of open-label treatment and 4 weeks

of post-treatment follow-up. De novo subjects will also have a screening/baseline period of up to 3 weeks and therefore a total duration of approximately 59 weeks.

3.1.6. Stopping Rules

3.1.6.1. Stopping Rules for Individual Subjects

For any subject discontinued from the study based on one of the stopping rules outlined in Section 3.1.6.1.1 or 3.1.6.1.2 , the associated event must be reported as an AE or SAE in the eCRF within 24 hours of awareness. Please refer to Section 9.4.1 for further instructions.

3.1.6.1.1. 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 Food and Drug Administration (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 9.2.2.

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 rises 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)

A flow diagram displaying the criteria for discontinuing treatment based on aminotransferase elevations is provided in Appendix 17.1 .

3.1.6.1.2. Suicidal Behavior and Ideation

The $\alpha_2\delta$ ligand class of medications has been associated with increased risk of suicidal thoughts or behavior (Section 9.2.1). 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 subjects have a YES response to any question on the C-SSRS at any visit (current or past), unless the subject falls into the "Possible Exception" category below:
  - Possible exception (applying to YES responses to C-SSRS Q1 and/or Q2 only):
  1. The benefit from continuation on the study medication significantly outweighs the risk of continuing the patient 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.

3.1.6.2. 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

3.2.1.1. For the Study

The dosage regimens of DS-5565 (15 mg QD and 15 mg BID) were selected based on the results of the completed Phase 2 study in the US of DS-5565 in subjects with DPNP (DS5565-A-U201) as well as dose optimization modeling and simulation. In the DS5565-A-U201 study, efficacy was observed across a dose range from 15 mg QD to 15 mg BID. To confirm the DS5565-A-U201 experience in subjects with FM and to determine whether subsets of subjects may respond better to 15 mg QD or 15 mg BID, both doses are being evaluated in the preceding Phase 3 studies (DS5565-A-E309, DS5565-A-E310, or DS5565-A-E311).

The results of the DS5565-A-U201 study (Section 1.1.1.5) suggest that 15 mg QD may be the minimum effective dose, while efficacy is similar but numerically better at the 15 mg BID dose compared to 15 mg QD. Overall, there were greater mean reductions from baseline to end-of-treatment (Week 5) in ADPS in the DS-5565 treatment groups compared to placebo, especially at the higher dose levels. The mean changes from baseline to Week 5 in ADPS were -2.04, -2.32, -2.66, -2.64, and -2.79 for the DS-5565 5 mg QD, 10 mg QD, 15 mg QD, 10 mg BID, and 15 mg BID treatment groups, respectively, compared to -1.86 for placebo. These treatment differences were statistically significant ($p<0.05$) at the DS-5565 15 mg QD, 10 mg BID, and 15 mg BID dose levels.

Both of the Phase 3 dose regimens (15 mg QD and 15 mg BID) have a safety profile that is consistent with the $\alpha_2\delta$ ligand class of drugs; AEs have generally been mild to moderate in severity (see the DS-5565 Investigator Brochure). The DS-5565 30 mg/day treatment arm will be titrated from 15 mg/day after three weeks to lower the potential risk of side effects in subjects who require the higher dose for effective pain relief. No dose adjustment will be made for subjects with mild renal impairment, as only small increases in area under the concentration time curve (AUC) (1.4-fold) and maximum plasma concentration (C_{max}) (24%) were observed in healthy subjects with mild renal impairment (CrCl 50 to 80 mL/min/1.73 m^2 [refer to DS-5565 Investigator Brochure]).

The data from DS5565-A-U201 were also modeled for insights into dose optimization. Efficacy was determined using weekly ADPS. A continuous bounded outcome score methodology was employed.[2] Two safety endpoints, dizziness and somnolence, were modeled. A time-to-(first) adverse event was modeled (hazard model) as well as severity of AE, conditional on having an event (ordered categorical). These were fitted independently.[3] According to this pharmacokinetic (PK)/pharmacodynamic (PD) modeling, total daily doses > 20 mg are required to achieve a difference in mean ADPS

of at least 1.0 point between DS-5565 and placebo. Total daily doses < 20 mg are not predicted to achieve this level of response. The predicted probability of achieving a true −1 ADPS difference for 30 mg/day (15 mg BID) is 0.501 (or about 50%) based on the model. A second dose (15 mg QD) was picked based on a lower target with an implied safety (i.e. lower risk of AEs such as dizziness) advantage.

A completed Phase 2 study in Asia (Japan, Korea, and Taiwan) of DS-5565 in subjects with DPNP (DS5565-A-J202) did not show statistically significant differences in mean changes in the primary efficacy parameter, ADPS, from baseline to end-of-treatment (Week 7) for the DS-5565 treatment groups (5 mg BID, 10 mg BID, and 15 mg BID) compared to placebo (Section 1.1.1.5). There was, however, a trend toward improvement for subjects treated with D-S5565 in terms of ADPS responder rate (i.e. proportion of subjects with ≥30% and ≥50% reduction in ADPS). The incidence of TEAEs showed potential dose-dependency (TEAEs occurred in 48.9% of subjects for the 5 mg BID group, 63.4% for the 10 mg BID group, and 73.3% for the 15 mg BID group).

3.2.1.2. For Individual Subjects

Subjects will be initiated at 15 mg QD. After 3 weeks of open-label treatment (i.e. at Visit 6), subjects may be titrated to 15 mg BID based on efficacy and safety criteria as detailed in Section 5.1.1. After a subject has been up-titrated to 15 mg BID, that subject may be down-titrated back to 15 mg QD based on efficacy and safety criteria as detailed in Section 5.1.1.

3.2.2. Control Treatments

No control treatments will be used in this study.

4. STUDY POPULATION

4.1. Enrollment

Subjects for this open-label extension study are those who completed participation (through the End-of-Tapering visit) in one of the preceding studies (DS5565-A-E309, DS5565-A-E310, or DS5565-A-E311) and agreed to rollover; In addition subjects who did not participate in a preceding double-blind study (referred to as de novo subjects) may be enrolled.

The investigator must inform each prospective subject of the nature of the study, explain the potential risks, and obtain written informed consent from the subject prior to performing any study-related screening procedures. For rollover subjects, signature of the informed consent document for this study should be obtained before the start of the End-of-Tapering visit (Week 14, Visit 13) of one of the preceding studies (DS5565-A-E309, DS5565-A-E310, or DS5565-A-E311). For additional information on informed consent, see Section 1.5.2.

The subject identification number used in the preceding study shall be retained for use in this study. Subjects who did not participate in a preceding study will be assigned a subject identification number. This subject identification number must be used for subject identification on all study-related documents (eCRFs, clinic notes, laboratory samples, etc.).

The user will need to supply the Interactive Voice Response/Interactive Web Response (IXRS) system with the information required by the system (e.g. site number, subject identification number).

A subject will be considered enrolled upon signature of the informed consent document for this study.

4.1.1. Inclusion Criteria

Subjects who completed one of the preceding Phase 3 DS-5565 study (DS5565-A-E309, DS5565-A-E310, or DS5565-A-E311)

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

1. Able to give written informed consent
2. Completed participation (i.e. completed the End-of-Tapering visit) in a preceding study of DS-5565 in FM (DS5565-A-E309, DS5565-A-E310, or DS5565-A-E311)
3. Women of child-bearing potential (WOCBP) must be using an adequate method of contraception (as detailed in Section 9.5) to avoid pregnancy during the study and for 4 weeks after study completion
4. The subject must not have experienced any significant safety issues during the preceding study that, in the investigator's judgment, would adversely impact the subject's well-being in the long-term extension

5. De Novo Subjects
6. Age ≥ 18 years
7. Able to give written informed consent
8. Able to complete subject-reported questionnaires per the investigator's judgment
9. At screening, subjects must meet the 1990 American College of Rheumatology (ACR) criteria for FM, i.e. widespread pain present for at least 3 months and pain in at least 11 of 18 specific tender point sites. In addition, the 2010 ACR criteria must be met:
10. Widespread pain index (WPI) ≥ 7 and symptom severity (SS) scale score ≥ 5, or WPI 3 to 6 and SS scale score ≥ 9
11. Symptoms have been present at a similar level for at least 3 months
12. The subject does not have a disorder that would otherwise explain the pain
13. ADPS of ≥ 4 on the 11-point numeric rating scale (NRS) over the past 7 days prior to first dose (based on completion of at least 4 daily pain diaries during the 7-day baseline period)
14. Subject must have documented evidence of a fundoscopic examination (with pupil dilation) or a scanning laser ophthalmoscopy examination within 12 months prior to screening or at screening
15. Women of child-bearing potential (WOCBP) must be using an adequate method of contraception (as detailed in the body of the protocol) to avoid pregnancy during the study and for 4 weeks after study completion

4.1.2. Exclusion Criteria

All Subjects

1. Clinically significant unstable neurologic, psychiatric, ophthalmologic, hepatobiliary, respiratory, or hematologic illness or unstable cardiovascular disease (e.g. severe hypotension, uncontrolled cardiac arrhythmia, or myocardial infarction) or any other concurrent disease during the preceding study (for rollover subjects) or within 12 months prior to screening (for de novo subjects) that in the opinion of the investigator would interfere with study participation or assessment of safety and tolerability
2. 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 questions about active suicidal ideation/intent/behaviors occurring within the past 12 months must be excluded (C-SSRS Suicide Ideation section – Questions 3, 4, or 5; C-SSRS Suicidal Behavior section, any of the suicide behaviors questions). Such subjects should be referred immediately to a mental health professional for appropriate evaluation.

3. Subjects who are unlikely to comply with the protocol (e.g. uncooperative attitude, inability to return for subsequent visits) and/or otherwise considered by the investigator to be unlikely to complete the study
4. Subjects with severe or uncontrolled depression that, in the judgment of the investigator, makes the subject inappropriate for entry into the study
5. Subjects with pain due to other conditions (e.g. DPNP or post-herpetic neuralgia) that, in the opinion of the investigator, would confound assessment or self-evaluation of the pain associated with FM
6. Subjects with pain due to any widespread inflammatory musculoskeletal disorder (e.g. rheumatoid arthritis, lupus) or widespread rheumatic disease other than FM.
7. Abuse or dependence of prescription medications, street drugs, or alcohol within the last 1 year
8. Any history of a malignancy other than basal cell carcinoma within the past 5 years
9. A diagnosis of untreated sleep apnea or initiation of treatment for sleep apnea within the past 3 months
10. Known hypersensitivity to $\alpha_2\delta$ ligands or other components of the study medications
11. Pregnancy or breast-feeding, or intent to become pregnant during the study period
12. Abnormal investigative tests (i.e. ECGs) and laboratory values judged by the investigator to be clinically significant at the End-of-Treatment visit (Visit 11, Week 13) in the preceding study (for rollover subjects) or at screening (for de novo subjects), with particular focus on:
    - Abnormal renal function defined as calculated CrCl < 60 mL/min determined by the central laboratory using the Cockcroft-Gault equation,[4] blood urea nitrogen> 1.5 × ULN; serum creatinine > 1.6 mg/dL (> 141.4 µmol/L); or
    - Abnormal liver function defined as AST (SGOT) > 2.0 × ULN, ALT (SGPT) > 2.0 × ULN; alkaline phosphatase > 1.5 × ULN; total bilirubin> 1.2 × ULN. If a subject has total bilirubin > 1.2 ULN, unconjugated and conjugated bilirubin fractions should be analyzed and only subjects documented to have Gilbert's syndrome may be enrolled; or
    - Creatine kinase > 3.0 × ULN

For De Novo Subjects Only

13. Unable to undergo pre-study washout of prohibited concomitant medications (as listed in Section 5.2.1 of the protocol)
14. 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 are excluded, but mild to moderate major depression or

anxiety disorders are permitted provided that the investigator assesses the patient as clinically stable and appropriate for entry into the study

15. Any diagnosis of lifetime bipolar disorder or psychotic disorder
16. Subject is currently enrolled in or has not yet completed at least 30 days since ending another investigational device or drug study or is receiving other investigational agents
17. Subject is an employee of the study center, an immediate family member* of an employee of the study center, or an employee of Daiichi Sankyo, INC Research, or any of the study vendors supporting this study. *(spouse, parent, child, or sibling, whether biological or legally adopted)

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 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 an approved contraception method 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 or sponge with spermicide, condom, intrauterine device or partner's vasectomy.

All female subjects, regardless of child-bearing potential, must have a negative serum pregnancy test at all clinic visits through to the End-of-Tapering visit. All incidence of borderline pregnancy tests (as reported by the central lab) at screening should be followed up to exclude pregnancy (Exclusion criteria 11). Exclusion criteria (Section 4.1.2) can be satisfied in the cases of

1. Documented permanent sterilization, methods which include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

2. Confirmation of postmenopausal status, with documented serum follicle stimulating hormone level >35 mIU/mL (with or without hormone replacement therapy) and no menses within the previous 12 months before Randomization Period.

A urine pregnancy test will be performed for all WOCBP at the Follow-Up clinic visit.

Daiichi Sankyo must be notified of any study subject who becomes pregnant while participating in this clinical study, as described in Section 9.5.

4.2. Removal of Subjects From Therapy

Data from all enrolled 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 3.1.6.1.2).

The MINI and C-SSRS are to be administered at any time during the study (including unscheduled visits) based on investigator's discretion (Section 3.1.6.1.2).

4.2.1. Reasons for Withdrawal/Early Discontinuation

If a subject discontinues from the study treatment for any reason, the reason for discontinuation or withdrawal must be recorded on the eCRF using the following criteria:

Subjects who did not complete one of the preceding Phase 3 DS-5565 studies (DS5565-A-E309, DS5565-A-E310, or DS5565-A-E311) and withdraw prior to start of treatment 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

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

- Adverse event
- Death
- Lack of efficacy
- Lost to follow-up
- Protocol violation
- Study terminated by sponsor
- Withdrawal by subject (indicate reason)
- Other (indicate reason)

If a subject is withdrawn due to requirement for a prohibited pain medication, the reason may be recorded as lack of efficacy, as appropriate. Reasons recorded under "protocol violation" may include failure to comply with protocol requirements or study procedures, pregnancy, etc.

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 should be withdrawn from the study and early termination study procedures performed.

All subjects who are withdrawn should complete protocol-specified withdrawal procedures (see Section 4.2.2 and Section 6.4).

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.

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 (Visit 21) procedures as soon as possible after early withdrawal (Section 6.4). All subjects who are withdrawn from the study should return for a post-treatment follow-up visit (Section 6.5).

4.2.3. Subject Replacement

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

4.2.4. Subject Rescreening Procedures

Rescreening of subjects will not be permitted.

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 product for this study is:

- DS-5565 15 mg tablets

5.1.1. Method of Assigning Subjects to Treatments and Blinding

Subjects entering into the open-label extension phase of the study will initially receive a 15 mg QD dose of DS-5565. After 3 weeks on the 15 mg QD dose (at Visit 6, Week 3), subjects will be asked about the adequacy of their pain control. Depending on their level of pain control and whether they have experienced any clinically relevant TEAEs since the previous visit, subjects may be dose-escalated to DS-5565 15 mg BID. The dose escalation criteria are defined in Table 5.1.

Table 5.1: Dose Escalation Criteria

Pain Control[a]	Clinically Relevant TEAE[b]	Dose Increase[c]
Inadequate	No	Yes
	Yes	No
Acceptable but not optimal	No	Yes
	Yes	No
Optimal	No	No
	Yes	No

[a] Based upon the investigator's judgment
[b] Any moderate or severe episode of dizziness or somnolence, any episode of edema or clinically significant weight gain, or any other clinically relevant (in the judgment of the investigator) TEAE since the previous visit
[c] Yes = subject may be dose-escalated to DS-5565 15 mg BID
Abbreviations: BID = twice daily, TEAE = treatment-emergent adverse event

Once a subject has been dose-escalated to 15 mg BID, continuation of the 15 mg BID dose will occur as long as pain control is adequate and the subject experiences no moderate or severe episode of dizziness or somnolence, edema, clinically significant weight gain, or any other clinically relevant (in the judgment of the investigator) AE. If the subject does experience a clinically relevant AE, then the following criteria will determine whether discontinuation or down-titration of the dose should occur:

- If the subject previously reported inadequate pain control with 15 mg QD dosing, the subject will be discontinued from the study
- If the subject previously reported acceptable pain control with 15 mg QD dosing, the subject may be dose-reduced to 15 mg QD

No blinding will be used.

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 subject identification number (SID).

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.

Contract research organization (CRO) personnel will review each subject's treatment compliance during investigational site visits and at the completion of the study.

5.1.3. Labeling and Packaging

DS-5565 tablets will be supplied in labeled blister cards (wallets) containing 15 mg tablets. The blister label will include all information required by federal and local regulations. Additional details on the investigational drug product, such as the expiration date, can be found in documentation accompanying drug shipment.

5.1.4. Preparation

Study drug will be provided to sites as fully prepared blister cards (wallets). All wallets will contain 15 mg tablets.

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.

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) and must contact Daiichi Sankyo Clinical Supply Operations personnel or designee to determine if the affected supplies can be used.

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, and sign the Receipt of Shipment Form provided. The original will be retained at the site. In addition, the Investigator or designee shall contact Daiichi Sankyo Clinical Supply Operations as soon as possible if there is a problem with the shipment.

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 enrolled 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 on site or returned to a designee as instructed by the sponsor. Investigational product will be returned only after the study monitor has completed a final inventory to verify the quantity to be returned. The return of investigational product must be documented and the documentation included in the shipment. 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).

All investigational product inventory forms must be made available for inspection by the sponsor's authorized representative (e.g. 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 efficacy and/or safety is not permitted. This is particularly important for analgesics and/or other medications or therapies that may be intended specifically as treatments for FM. Subjects should be instructed not to take any prohibited analgesic medicine, as listed in Table 5.2 , during the study. Use of prohibited medications may necessitate subject discontinuation from the study.

De novo subjects (i.e. subjects who did not complete a preceding study) who are receiving medication for FM (or any prohibited medication listed in Table 5.2) will be required to undergo drug washout prior to the Baseline visit. The investigator should comply with product labeling instructions for drug discontinuation (e.g. tapering of opioids to avoid side effects related to dependence). Minimum washout requirements for specific classes of prohibited medications are provided in Table 5.2.

De novo subjects receiving treatment for FM should not begin washout of pain medication until they are determined to be potentially eligible for the study (based on the results of the Visit 1 assessments) by the investigator and contacted via telephone by the investigator or designee. After the Washout Period is complete, de novo subjects will return to the site for the Baseline visit (Visit 3).

Table 5.2: Prohibited Medications and Treatments

Medication Class/Example Drugs	Minimum Washout Period Prior to Collection of Baseline Pain Assessments[a]
Anticonvulsants, including pregabalin and gabapentin	3 days
Opioids, including tramadol; tapentadol	7 days
COX-2 inhibitors	3 days
Benzodiazepines	7 days
Dopamine agonists	7 days
Tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors and other antidepressants except for allowed SSRIs as shown in Table 5.3.	7 days
Non-benzodiazepine hypnotics, such as zolpidem, skeletal muscle relaxants (carisoprodol, cyclobenzaprine, tizanidine, etc), topical capsaicin, topical or injected local anesthetics, tender point injections, fatty acid supplements, and memantine	7 days

[a] Washout period only applies to de novo subjects who do not transition from a preceding study. Investigators should also comply with product labeling recommendations for drug discontinuation.

Nonpharmacological therapies for FM, such as acupuncture, laser therapy, spinal cord stimulation, electrical nerve stimulation, or surgery, or any other pharmacological treatment designed to modulate the perception of pain, are also prohibited during the study with the exception of the allowable medications listed in Section 5.2.2. Sedating antihistamines for sleep, melatonin, cannabinoids, and other sedatives (e.g. barbiturates) are also prohibited.

Changes to normal daily exercise routines are allowed according to investigator judgment. Subjects may continue with some stable nonpharmacological therapies, such as physiotherapy, massage, chiropractor, and psychological therapies.

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. Main Allowable Medications

Use of SSRIs (but not serotonin-norepinephrine reuptake inhibitors [SNRIs]) is allowed if the subject has been on a stable dose during the preceding study (or for ≥ 2 months prior to screening for a de novo subject) and is not anticipated to need adjustment during the study period. Examples of allowed SSRIs are provided in Table 5.3.

Table 5.3: Common Allowed SSRIs

Examples of Permissible SSRIs	
Citalopram	Dapoxetine
escitalopram	fluoxetine
Fluvoxamine	paroxetine
Sertraline	vilazodone
Note: Any other approved SSRI in each participating country (i.e. generics, etc) not included in this list will also be allowed if maintained at stable doses over the last two months prior to study entry	

Aspirin (up to 160 mg/day) for myocardial infarction and stroke prophylaxis is permitted. The use of acetaminophen/paracetamol (up to 2 grams/day in divided doses at intervals of 4-6 hours) will also be permitted as allowable (rescue) medication for breakthrough FM.

The use of all pain-related medications including acetaminophen/paracetamol or any nonsteroidal anti-inflammatory drugs (NSAID) must be documented as a concomitant medication. The reason or indication for its use, if not likely related to FM based on investigator judgment, should also be recorded as an AE in the eCRF. The subject should be instructed on risks associated with acetaminophen overdose. Other NSAIDs such as ibuprofen and naproxen may be used for any pain indication (e.g. headache, back pain) except for breakthrough FM. NSAID use for breakthrough FM is not permitted.

Any non-pain-related, 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 experience, as appropriate, and the dose, route of administration, start and End-of-Treatment, and other relevant information (e.g. reason for use) should be documented.

Birth control medications and hormone replacement therapy are permitted.

6. STUDY PROCEDURES

A study visit schedule in tabular format is provided in Appendix Section 17.3.

Subjects will receive open-label treatment for 52 weeks followed by 4 weeks of post-treatment follow-up. The screening/baseline process will depend on whether the subject is a rollover subject or de novo subject. De novo subjects will have a Screening visit (Visit 1) and also complete Visits 2 and 3 (as detailed in Section 6.1.2) before receiving study treatment at the Start-of-Treatment visit (Visit 4). Rollover subjects will have screening procedures performed at the Start-of-Treatment visit (Visit 4), which will occur on the same day as the End-of-Tapering visit of the preceding study (as detailed in Section 6.2.1). All subjects will visit the clinic the following week (Visit 5, Week 1); every 2 weeks thereafter for the next 12 weeks (Weeks 3, 5, 7, 9, 11, and 13); 3 weeks thereafter (Week 16); every 4 weeks thereafter for the remainder of the study (Weeks 20, 24, 28, 32, 36, 40, 44, 48, and 52); and at the post-treatment follow-up visit (Visit 23, Week 54). Post-treatment follow-up will also include telephone contacts at 3 days (Visit 22) and at 4 weeks (Visit 24) after the subject's last dose of study treatment.

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 3.1.6.1.2).

6.1. Screening/Baseline for De Novo Subjects

Visits 1 to 3 are required only for de novo subjects.

For de novo subjects, the Screening Period will include a Screening visit (Visit 1), a telephone contact prior to the drug Washout Period (for subjects who are receiving prohibited medications) (Visit 2), and a Baseline visit (Visit 3). The duration of the Screening Period will be approximately 3 weeks, but no longer than 35 days.

Subjects receiving 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 5.2 for minimum washout requirements). However, these subjects will be requested not to begin washout of pain medication until they are determined to be potentially eligible (based on the results of the Visit 1 assessments) 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 prohibited medication and date of last administration will be recorded on the eCRF.

The subject will receive an electronic diary at the Baseline visit. The subject will complete the electronic diary at home for 7 days prior to initiating study treatment.

Fasting is not required prior to the Screening or Baseline visits.

6.1.1. Screening Visit for De Novo Subjects (Visit 1; Week -3, Prior to Enrollment)

The initial Screening visit should occur no more than 35 days prior to the Start-of-Treatment 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 (Visit 1):

- Obtain written informed consent prior to performing any of the formal screening procedures.
- Administer the WPI and SSS diagnostic questionnaires
- Administer the M.I.N.I Version 6.0 interview
- Administer the C-SSRS (See Section 9.2.1)
- 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 complete physical examination, including fundoscopy examination with pupil dilation or a scanning laser ophthalmoscopy examination (Section 9.9.2)
- Perform a 12-lead ECG (Section 9.8)
- Collect blood and urine samples for evaluation of standard laboratory safety tests (chemistry, hematology, and urinalysis). The central laboratory will perform a serum pregnancy test on all female subjects regardless of child-bearing potential
- Subjects will be excluded for screening laboratory values judged by the investigator to be clinically significant, with a particular focus on the limits in Table 6.1.

Table 6.1: Screening Laboratory Values

Blood Chemistry	AST (SGOT)	> 2.0 × ULN
	ALT (SGPT)	> 2.0 × ULN
	Alkaline phosphatase	> 1.5 × ULN
	Total bilirubin	> 1.2 × ULN[a]
	Blood urea nitrogen	> 1.5 × ULN
	Creatine kinase	> 3.0 × ULN
	Serum creatinine	> 1.6 mg/dL (> 141.4 µmol/L)
	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 (SGPT) = alanine aminotransferase, AST (SGOT) = aspartate aminotransferase, CrCl = creatinine clearance (determined by the central laboratory using the Cockcroft-Gault equation), ULN = upper limit of normal

- 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 5.2 ; instruct subjects not to begin washout until notified by phone they have satisfied all eligibility requirements (e.g. documenting satisfactory laboratory results)
- Provide instructions on prohibited medications
- Contact IXRS to register the subject and obtain SID

6.1.2. Washout Telephone Contact for De Novo Subjects (Visit 2; Week -2, Prior to Enrollment)

When a de novo subject's potential eligibility is determined based on the results of the Visit 1 assessments, the site will contact the subject by telephone. If the subject is eligible and does not require washout, the Start of Treatment Visit will be scheduled. If the subject is eligible and currently on a prohibited medication (see Table 5.2), the following activities and/or assessments will be performed during this telephone contact:

- Assess for and record AEs and concomitant medication use
- Provide instructions on washout of prohibited medication(s), including the duration of the Washout Period (per Table 5.2)

6.1.3. Baseline Visit for De Novo Subjects (Visit 3; Week -1, Prior to Enrollment)

After the washout period (if applicable), de novo subjects will return to the clinic for a Baseline visit. The following activities and/or assessments will be performed:

- Assess for and record AEs
- Assess for and record concomitant medication use including allowable analgesics
- Provide subjects with electronic daily diaries and instructions for recording baseline pain and sleep interference ratings every morning and any allowable pain-related medications. The subject should begin diary completion the following morning

6.2. Start-of-Treatment Visit (Visit 4; Week 0)

The procedures to be performed at the Start-of-Treatment visit depend on whether the subject is a rollover subject or a de novo subject.

6.2.1. Start-of-Treatment Visit for Rollover Subjects

For rollover subjects, the Start-of-Treatment visit (Visit 4) will be conducted on the same day of the End-of-Tapering visit of the preceding study to avoid interruption in treatment with study drug. Signature on the informed consent document for this study should be obtained before the start of the End-of-Tapering visit (Week 14, Visit 13) of the preceding study.

It should be noted that results from safety laboratory tests from the End-of-Treatment visit of the preceding study are required to determine eligibility. Subjects will be excluded for laboratory values exceeding limits listed in Table 6.2.

Table 6.2: Required Laboratory Values (from the End-of-Treatment Visit of the Preceding Study)

Blood chemistry	AST (SGOT)	> 2.0 × ULN
	ALT (SGPT)	> 2.0 × ULN
	Alkaline phosphatase	> 1.5 × ULN
	Total bilirubin	> 1.2 × ULN[a]
	Blood urea nitrogen	> 1.5 × ULN
	Creatine kinase	> 3.0 × ULN
	Serum creatinine	> 1.6 mg/dL (> 141.4 µmol/L)
	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 (SGPT) = alanine aminotransferase, AST (SGOT) = aspartate aminotransferase, CrCl = creatinine clearance (determined by the central laboratory using the Cockcroft-Gault equation), ULN = upper limit of normal

The following activities and/or assessments will be performed at/during the Start-of-Treatment visit (Visit 4) in this study:

- Obtain written informed consent (before the start of the End-of-Tapering visit in the preceding study)
- Assess all applicable inclusion and exclusion criteria
- Perform complete physical examination (Section 9.9.2)
- Perform a 12-lead ECG (Section 9.8)
- Ask subject to complete the HADS, SF-36 and EQ-5D questionnaires
- Contact IXRS to register the subject and obtain new study medication wallet number
- Dispense study medication and review dosing instructions. The first dose of study medication is to be taken on the same day as the Start of Treatment visit, at bedtime after completion of the study visit. Subjects should be instructed to bring their study medication wallet with them to each clinic visit

Information collected during the preceding study will also be utilized in this extension study. This information includes:

- Demographic information (collected at Screening of the preceding study)
- Medical/surgical history (collected at Screening of the preceding study)
- AEs (any ongoing AEs from the preceding study will be transferred to the database for this extension study)
- Concomitant medications (any ongoing concomitant medications from the preceding study will be transferred to the database for this extension study)
- Vital signs (collected at the End-of-Tapering visit of the preceding study)
- Height (collected at Screening of the preceding study)
- Weight (collected at the End-of-Tapering visit of the preceding study)
- C-SSRS (collected at the End-of-Tapering visit of the preceding study (See Section 9.2.1)
- Clinical laboratory tests (collected at the End-of-Tapering visit of the preceding study)
- Pregnancy test (collected at the End-of-Tapering visit of the preceding study)
- Pain scores (recorded for 7 days prior to the End-of-Tapering visit of the preceding study)

- Sleep interference scores (recorded for 7 days prior to the End-of-Tapering visit of the preceding study)

6.2.2. Start-of-Treatment Visit for De Novo Subjects

For de novo subjects, the following activities and/or assessments will be performed at the Start-of-Treatment visit (Visit 4; Week 0).

- Assess for and record AEs
- Record any concomitant medications used since the last visit
- Review subject's electronic daily diary data and ask subject to complete pain and sleep interference ratings for today (Day 1), if not yet completed
- Assess subject eligibility using the study's inclusion/exclusion criteria, including Baseline ADPS from daily diaries (a minimum of 4 daily pain ratings must be available)
- Administer the C-SSRS and evaluate for eligibility (See Section 9.2.1)

If the subject is found to be eligible based on the results of the ADPS and C-SSRS assessments, proceed to perform the following procedures:

- Record body weight and vital signs (temperature, heart rate, supine and orthostatic blood pressure)
- Perform abbreviated physical examination (see Section 9.9.2)
- Collect blood and urine samples for evaluation of standard laboratory safety tests (chemistry, hematology and urinalysis). An additional 8.5 mL serum separating tube of blood will be collected at Day 1 and stored for further analysis in the event of AST or ALT elevations $\geq$ 3 X ULN during the study (see Section 9.2.2)
- The central laboratory will perform a serum pregnancy test on all female subjects regardless of child-bearing potential
- Ask subject to complete the HADS, SF-36 and EQ-5D questionnaires
- Provide additional training on recording of pain and sleep interference ratings for any subjects who had errors or missing information during the Baseline Period
- Contact IXRS to obtain the subject 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 Start of Treatment visit, at bedtime after completion of the study visit. Subjects should be instructed to bring their study medication wallet with them to each clinic visit

6.3. On-Treatment Period (Visits 5 to 20; Weeks 1 to 48)

The following activities and/or assessments will be performed at all On-Treatment visits (except where otherwise noted):

- Assess for and record AEs
- After 3 weeks on the 15 mg QD dose (at Visit 6, Week 3), subjects will be asked about the adequacy of their pain control and may be dose-escalated to DS-5565 15 mg BID (see Section 5.1.1)
- Assess for and record concomitant medication use including allowable analgesics
- Review instructions with the subject for completion of the pain and sleep interference diary. Note: These instructions need to be reviewed with the subject only at Visit 10 (Week 11), Visit 13 (Week 20), Visit 16 (Week 32), Visit 19 (Week 44), and Visit 20 (Week 48)
- Review electronic diary data from the previous week. Note: These data need to be reviewed only at Visit 11 (Week 13), Visit 14 (Week 24), Visit 17 (Week 36), Visit 20 (Week 48), and Visit 21 (Week 52)
- Collect study medication wallets and review medication compliance
- Record vital signs (temperature, heart rate, supine and orthostatic blood pressure) and body weight
- Complete the C-SSRS and evaluate for continued eligibility (See Section 9.2.1)
- Perform an abbreviated physical examination for all subjects; perform a fundoscopy examination without pupil dilation or a scanning laser ophthalmoscopy examination at Visit 14 (Week 24) for de novo subjects (see Section 9.9.2)
- Collect non-fasting blood and urine samples for evaluation of standard laboratory safety tests (chemistry, hematology, and urinalysis). The central laboratory will perform a serum pregnancy test on all female subjects regardless of child-bearing potential
- Contact IXRS and obtain new study medication wallet number (as needed)
- Dispense study medication and review dosing instructions. At Visit 20 (Week 48), subjects should be instructed to take all study medication, as scheduled, up until the day of their End-of-Treatment visit (Visit 21, Week 52), but not on the morning of Visit 21 (i.e. subjects should complete dosing on the evening prior to their End-of-Treatment visit)

6.4. End-of-Treatment/Early Termination (Visit 21; Week 52)

The following activities and/or assessments will be performed at the End-of-Treatment or Early Termination visit (Visit 21). No fasting is required prior to the End-of-Treatment visit.

- Assess for and record AEs
- Assess for and record concomitant medication use including allowable analgesics
- Review electronic diary data and collect electronic diary
- Collect study medication and review medication compliance
- Record vital signs (temperature, heart rate, supine and orthostatic blood pressure) and body weight
- Collect blood and urine samples for evaluation of standard laboratory safety tests (chemistry [hematology, and urinalysis). The central laboratory will perform a serum pregnancy test on all female subjects regardless of child-bearing potential
- Ask the subject to complete the PGIC, HADS, SF-36 and EQ-5D questionnaires
- Complete the C-SSRS (See Section 9.2.1)
- Perform complete physical examination for all subjects, including a fundoscopy examination with pupil dilation or a scanning laser ophthalmoscopy examination for de novo subjects only (see Section 9.9.2)
- Perform a 12-lead ECG (Section 9.8)
- Update IXRS with subject status

6.5. Follow-Up

6.5.1. Post-Treatment Follow-Up (Visits 22 to 24; Weeks 52 to 56)

6.5.1.1. Telephone Contact at Day 3 of Follow-up (Visit 22; Week 52.5)

All subjects, including those who discontinue prematurely, will be contacted by telephone 3 days after the subject's last dose of study treatment. The following activities and/or assessments will be performed at this 3-day follow-up telephone contact:

- Assess for and record AEs
- Assess for and record concomitant medication use including allowable analgesics
- Administer the PWC

6.5.1.2. Visit at Week 2 of Follow-up (Visit 23; Week 54)

All subjects then will return to the clinic for post-treatment follow-up approximately 14 (± 3) days following the last dose of study medication.

The following activities and/or assessments will be performed at the Follow-up clinic visit (Visit 23, Week 54):

- Assess for and record AEs
- Assess for and record concomitant medication use including allowable analgesics
- Record vital signs (temperature, heart rate, supine and orthostatic blood pressure) and body weight
- Perform urine pregnancy test on all WOCBP and confirm negative
- Administer the C-SSRS(See Section 9.2.1)
- Administer the PWC

Any abnormal findings (including abnormal laboratory values) observed at the End-of-Treatment visit should be rechecked at the Follow-up visit. Further safety assessments may be required for clinically significant abnormal findings observed at the Follow-up visit.

6.5.1.3. Telephone Contact at Week 4 of Follow-up (Visit 24; Week 56)

All subjects will be contacted by telephone approximately 4 weeks following the last dose of study medication. The following activities and/or assessments will be performed at this 4-week follow-up telephone contact:

- Assess for and record AEs
- Assess for and record concomitant medication use including allowable analgesics

6.6. Protocol Deviations

The investigator should conduct the study in compliance with the protocol agreed to by Sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the 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. Sponsor must be notified of all intended or unintended deviations to the protocol (e.g. inclusion/exclusion criteria, dosing, missed study visits) on an expedited basis.

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

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

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

7. EFFICACY ASSESSMENTS

7.1. Average Daily Pain Score (ADPS)

Subjects will record their worst pain over the previous 24 hours in an electronic diary using an 11-point numeric rating scale (NRS) ranging from 0 (no pain) to 10 (worst possible pain) (refer to the Study Manual for a copy of this instrument). Pain diary scores will be recorded by the subjects during the 7 days prior to Visit 11 (Week 13), Visit 14 (Week 24), Visit 17 (Week 36), Visit 20 (Week 48), and Visit 21 (Week 52). For de novo subjects only, pain diary scores will be recorded during the 7 days prior to Visit 4 (Start-of-Treatment). During the 7 days prior to these visits, every day upon awakening, prior to taking study medication, the subject should indicate the number that best describes his or her worst pain over the previous 24 hours.[5]

For rollover subjects, the ADPS value taken from the last visit of the DS5565-A-E309, DS5565-A-E310, or DS5565-A-E311 study (i.e. End-of-Tapering) will be used as the baseline score for this study and hence will not be repeated by the subject at Visit 4 (Start-of-Treatment).

For de novo subjects, the baseline ADPS value will be calculated based on the subject's recording of pain diary scores during the Baseline period.

7.2. Patient Global Impression of Change (PGIC)

Subjects will complete the PGIC at the End-of-Treatment/Early Termination visit.

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.[6] 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. Hospital Anxiety and Depression Scale (HADS)

All subjects will complete the HADS questionnaire at the Start-of-Treatment visit (Visit 4) and at the End-of-Treatment/Early Termination visit.

The HADS questionnaire is a reliable, widely-used self-assessment scale to assess symptoms of anxiety and depression.[7] The instrument consists of 7 questions related to anxiety and 7 related to depression, each rated on a 4-point scale (score of 0 to 3). Scores for anxiety and depression are independently summed to compute HADS-Anxiety and HADS-Depression subscale scores, with ranges from 0 to 21, where higher scores indicate greater severity.

7.4. EuroQol Instrument 5 Dimensions (EQ-5D)

All subjects will complete the EQ-5D questionnaire at the Start-of-Treatment visit (Visit 4) and at the End-of-Treatment/Early Termination visit. The EQ-5D (refer to the Study

Manual for a copy) is a well-standardized instrument that shows high construct validity and responsiveness in patients with chronic pain[8] and has been used specifically in FM.[9] The EQ-5D includes a descriptive section with 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) that are combined into an overall health utilities index, and an NRS (100 mm VAS) that measures perception of overall health, with 0 indicating worst health and 100 representing best imaginable health.

7.5. Short Form 36 (SF-36)

All subjects will complete the SF-36 questionnaire at the Start-of-Treatment visit (Visit 4) and at the End-of-Treatment/Early Termination visit. The SF-36 (refer to the Study Manual for a copy) is a generic health survey that asks 36 questions to measure functional health and well-being from the subject's point of view. It is a practical, reliable, and valid measure of physical and mental health widely used across various disease areas, including FM.[10] The SF-36 provides scores for 8 health domains (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health) as well as psychometrically-based physical component summary (PCS) and mental component summary (MCS) scores. All health domain scales contribute to the scoring of both the PCS and MCS measures.

7.6. Average Daily Sleep Interference Score (ADSIS)

Pain-associated sleep interference will be assessed using electronic diaries using an 11-point NRS ranging from 0 (pain does not interfere with sleep) to 10 (pain completely interferes with sleep, unable to sleep) (refer to the Study Manual for a copy of this instrument). The sleep interference NRS is a standard tool used to assess how pain has interfered with sleep during the past 24 hours. Sleep interference scores will be recorded by the subjects during the 7 days prior to Visit 11 (Week 13), Visit 14 (Week 24), Visit 17 (Week 36), Visit 20 (Week 48), and Visit 21 (Week 52). For de novo subjects only, sleep interference scores will be recorded during the 7 days prior to Visit 4 (Start-of-Treatment). During the 7 days prior to these visits, every day upon awakening, prior to taking study medication, the subject should complete the sleep interference question along with the pain question in the diary.

For rollover subjects, the sleep interference value taken from the last visit of the DS5565-A-E309, DS5565-A-E310, or DS5565-A-E311 study (i.e. End-of-Tapering) will be used as the baseline score for this study and hence will not be repeated by the subject at Visit 4 (Start-of-Treatment).

For de novo subjects, the baseline sleep interference value will be calculated based on the subject's recording of sleep interference scores during the Baseline period.

8. PHARMACOKINETIC ASSESSMENTS

8.1. Pharmacokinetic (PK) Variable(s)

Not applicable.

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 (defined in Section 9.3) occurring after the subject has signed the ICF and up to 4 weeks after the last dose of study medication (i.e. the follow-up period), whether observed by the investigator or reported by the subject, will be recorded on the AE eCRF page. For subjects rolled over from a preceding study (DS5565-A-E309, DS5565-A-E310, or DS5565-A-E311), any AE that is ongoing at the start of this study will be recorded as an AE in this study, and all AEs (new or from a preceding study) will be followed until resolution. For these rolled-over subjects, all AEs will be evaluated in the context of their experience in the preceding study.

All 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 9.2].

All SAEs are to be reported according to the procedures in Section 9.4 (SAE Reporting-Procedure for Investigators). 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 SAE narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report 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). Pre-planned (prior to signing the ICF) procedures or hospitalizations for pre-existing conditions which do not worsen in severity should not be reported as SAEs (see Section 9.3 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 should determine whether any AEs have occurred by evaluating the subject. AEs may be directly observed, reported spontaneously by the subject, or by questioning the subject at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 9.3. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature.

Investigators should follow subjects with AEs until the event has resolved or the condition has stabilized. Unresolved AEs, including significant abnormal laboratory values at the end of the study, should be followed up until resolution or until no longer clinically relevant.

9.2. Events of Special Interest

All antiepileptic drugs carry a risk of increased suicidal behavior and ideation. Furthermore, as mentioned in Section 3.1.6, increased hepatic transaminases have been observed in the DS-5565 development program and will be treated as AESIs.

9.2.1. 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 subjects receiving these drugs.[11]

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 baseline 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 (applying to yes responses to C-SSRS Q1 and/or 2 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.

9.2.2. Liver Enzyme Elevations/Liver Dysfunction

As described in Section 3.1.6.1.1, 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 (Section 11.10). In cases of liver laboratory abnormalities, it is important to ensure that the nature and the extent of liver injury is identified and study subjects are monitored until the liver laboratory assessments return to normal. Subjects who have any transaminase elevation associated with a clinical presentation suggestive of liver injury (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, 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 (NASH); hypoxic/ischemic hepatopathy; and biliary tract disease
- Obtain a history of exposure to environmental chemical agents
- Perform additional laboratory liver tests (e.g. serum lactate dehydrogenase, alkaline phosphatase, 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 9.4.1), 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).[12] 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 3.1.6.1.1.

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

- Gastroenterology or hepatology consultation
- Hepatobiliary ultrasound

9.3. Definitions

9.3.1. Adverse Event (AE)

An AE is defined as any untoward medical occurrence in a patient (or study subject) who has received a pharmaceutical product; an AE does not necessarily have to have a causal relationship with this treatment. An AE can be any unfavorable or unexpected sign (e.g. an abnormal laboratory finding), 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 each investigator, based on his/her knowledge and experience, to determine whether a sign, symptom or abnormal finding should be considered an AE.

9.3.2. Serious Adverse Event (SAE)

An SAE is defined as 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) surgeries or hospitalizations for pre-existing conditions which do not worsen in severity are not SAEs.

9.3.3. Adverse Event Severity

The following definitions should be used to assess severity 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.

9.3.4. Causality Assessment

The relationship between an AE and the study products will be determined by the investigator on the basis of his/her clinical judgment and the following definitions:

- 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 (e.g. 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 (e.g. disease under study, concurrent diseases, and concomitant medications).

9.3.5. Action Taken Regarding the Investigational Product

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

9.3.6. Adverse Event Outcome

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

9.3.7. Other Action Taken for Event

Other Action Taken for Event will be reported as one of the following:

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

9.4. Serious Adverse Event Reporting Procedure for Investigators

9.4.1. Reporting by Investigators

All AEs, SAEs, endpoints, and events of special interest, will be reported in the eCRF.

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

- SAEs (see Section 9.3.2 for definition)

- Hepatic events meeting combination abnormalities [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 per Section 3.1.6.1

All events (serious and non-serious) must be reported with investigator's assessment of the event's seriousness, severity, and causality to 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 eCRF to provide the most complete data possible within each follow-up.

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

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

9.4.2. Notifying Regulatory Authorities, Investigators, and Institutional Review Boards/Institutional Ethics Committees

Daiichi Sankyo and/or designee will inform investigators, IRBs/IECs, and regulatory authorities of any suspected unexpected serious adverse event 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 the Sponsor's instruction.

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

9.5. 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 via the Exposure in Utero (EIU) Reporting form (please contact your study monitor to receive the form). 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 a 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 9.4. Elected abortion is a procedure and should be reported following the definitions and procedures for reporting AEs or SAEs.

9.6. Clinical Laboratory Evaluations

Blood and urine samples for clinical laboratory evaluations will be shipped to a central laboratory for analysis. Results of all laboratory tests will be reported in the subject's eCRF or merged electronically with the clinical database (see Appendix 17.3).

9.6.1. Hematology

A single 2 mL ethylenediaminetetraacetic acid (EDTA) tube of blood will b

e drawn for the hematology assessments listed in Table 9.1. These will be measured from samples obtained at the Screening/Baseline visit, Treatment visits, and End-of-Treatment/Early Termination visit.

Table 9.1: Hematology Analytes

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

9.6.2. Blood Chemistry

A 2.5 mL serum separating tube of blood will be drawn for the blood chemistry assessments listed inTable 9.2. These will be measured from samples obtained at the Screening/Baseline visit, Treatment visits, and End-of-Treatment/Early Termination visit.

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
Alkaline phosphatase	Triglycerides
Total bilirubin[a]	

[a] Total bilirubin should be fractionated at baseline and whenever total bilirubin > 2 x ULN
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal

9.6.2.1. Estimation of Creatinine Clearance

Creatinine clearance (CrCl) will be estimated from serum creatinine by the central laboratory using the Cockcroft-Gault equation (Appendix 17.2).

9.6.3. Urinalysis

Standard urinalysis including a microscopic examination will be conducted for all subjects at the Screening visit, Treatment visits, and End-of-Treatment/Early Termination visit (Table 9.3).

Table 9.3: Urinalysis Determinations

Specific gravity	Blood
pH	RBC
Protein	WBC
Glucose	Bilirubin
Ketones	Urobilinogen

Abbreviations: RBC = red blood cell; WBC = white blood cell

For samples with findings on macroscopic analysis, microscopic examination for red blood cells (RBCs), white blood cells (WBCs), bacteria, and casts should be performed.

9.6.4. Pregnancy Testing

A serum pregnancy test will also be performed for all women at all clinic visits through the End-of-Treatment/Early Termination visit. A urine pregnancy test will be performed for all WOCBP at the Follow-up clinic visit.

9.7. Vital Signs

Vital signs will be recorded at all visits 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 manometer 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 that was used in the preceding study. For subjects not completing a preceding study, 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.

9.8. Electrocardiograms

A 12-lead ECG will be conducted at the Screening visit (Visit 1) for de novo subjects, and at Start-of-Treatment visit (Visit 4) and at the End-of-Treatment/Early Termination visit (Visit 21) for all subjects. 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). Refer to Section 9.1 for general guidance on when to report abnormal findings as AEs.

9.9. Physical Findings

9.9.1. Body Height and Weight

For de novo subjects only, measurement of height will be performed at the Screening visit (Visit 1) with the subject in a standing position and with shoes removed. The subject's knees should be straightened, head held erect, with eyes forward.

Measurement of weight should be performed at every visit, except the Baseline visit (Visit 3) for de novo subjects, with the subject dressed in indoor clothing, shoes removed. Subjects should be weighed on the same scale at all visits.

9.9.2. 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 (Visit 1) for de novo subjects or at the Start-of-Treatment visit (Visit 4) for rollover

subjects and End-of-Treatment/Early Termination visit (Visit 21) for all subjects. An abbreviated physical examination will be performed at the Treatment visits.

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 de novo subjects, a fundoscopy examination of the eyes, with pupil dilation or a scanning laser ophthalmoscopy examination, will be conducted at the Screening visit (Visit 1) and End of Treatment visit (Visit 21) during the full physical examination. At Visit 14 (Week 24), the abbreviated physical examination will include a fundoscopy examination without pupil dilation or a scanning laser ophthalmoscopy examination.

The abbreviated physical examination should minimally include clinical evaluations of the heart and lungs. Additional systems may be examined based on any symptoms exhibited by the subject.

9.10. Other Safety Assessments

9.10.1. Columbia-Suicide Severity Rating Scale (C-SSRS)

For rollover subjects, the C-SSRS assessment taken from the last visit of the DS5565-A-E309, DS5565-A-E310, or DS5565-A-E311 study (i.e. End-of-Tapering) will be used as the baseline assessment for this study and hence will not be repeated by the subject at Visit 4 (Start-of-Treatment).

For all other clinic visits (not including telephone visits), the C-SSRS will be administered by the investigator or a qualified designee trained in its administration using the study-specific tablet.

The C-SSRS is a standardized instrument that was developed to assess the severity of and monitor changes in suicidal ideation and behavior. [13] 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 nonsuicidal 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.

9.10.2. Physician Withdrawal Checklist (PWC)

The PWC will be administered by the investigator or designee using the study-specific tablet at the Post-treatment Follow-up visit. In addition, the PWC will be administered by telephone 3 days after the subject's last dose of medication.

Although developed specifically to measure symptoms of benzodiazepine withdrawal,[14] the PWC also has been used in studies of pregabalin.[15,16,17] 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 are 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 visit.

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

11.2. General Statistical Considerations

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

Raw data will be presented with the same precision with which they were collected.

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

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

For variables expressed as percent, 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 enrolled analysis set according to treatment assignment in the preceding study (as applicable). Continuous demographic variables (age [calculated from date of birth to the date of first dose], weight, height, and body mass index) for all enrolled subjects will be summarized with descriptive statistics. Categorical demographic variables (gender, race, ethnicity, and age group [e.g. non-elderly, elderly, very elderly]) will be summarized with frequency counts and corresponding percentages.

Subject disposition will be summarized for the enrolled analysis set according to treatment assignment in the preceding study (as applicable). The number of subjects screened, the number enrolled, and the number and percent of those who completed the

open-label extension period or withdrew (with the latter summarized by reason for withdrawal) will be summarized.

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

11.4. Efficacy Analyses

For ADPS, absolute values and changes from baseline will be summarized using the safety analysis set.

For PGIC, the proportions of subjects who are "minimally improved or better" (i.e. score ≤ 3) and of subjects who are "much improved or better" (i.e. score ≤ 2) will be summarized using the safety analysis set.

For the HADS, absolute values and changes from baseline for the Depression and Anxiety subscales will be summarized using the safety analysis set.

For the EQ-5D, absolute values and changes from baseline for the EQ-5D single summary index (based on the 5 domain questions) and the EQ VAS will be summarized using the safety analysis set.

For the SF-36, absolute values and changes from baseline for eight domains (i.e. physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health) as well as PCS and MCS scores will be summarized using the safety analysis set.

11.5. Pharmacokinetic/Pharmacodynamic Analyses

Not applicable.

11.6. Safety Analyses

The safety analysis set will be used for all safety analyses. For safety endpoints, the data from AE assessments, clinical laboratory assessments, physical examinations, 12-lead ECGs, vital signs (including weight) assessments, the C-SSRS evaluation, and the PWC evaluations will be summarized. Preceding study and extension study data will be summarized separately and also may be combined.

11.6.1. Adverse Event Analyses

AEs will be tabulated 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. For subjects who transfer directly into this study from a preceding study (DS5565-A-E309, DS5565-A-E310, DS5565-A-E311), an AE that started in the preceding study will not be considered treatment-emergent in this study unless the AE worsens in severity during this study. The frequency of subjects experiencing a specific TEAE will be tabulated by system organ class, preferred term, seriousness (see Section 9.3.2), worst severity (see Section 9.3.3), and relationship to study drug (see Section 9.3.4). 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 Evaluation 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. Shift tables (in categories of low, normal, and high, when appropriate) will be provided. 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.

11.6.4. Electrocardiogram Analyses

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

11.6.5. Physical Examinations

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

11.6.6. Columbia-Suicide Severity Rating Scale (C-SSRS)

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

11.6.7. Physician Withdrawal Checklist (PWC)

PWC data will be listed and summarized.

11.7. Other Analyses

Not applicable.

11.8. Interim Analyses

The sponsor expects that approximately 500 subjects across the development program for DS-5565 will need to be exposed to DS-5565 for at least 52 weeks to support registration. If this open-label extension study (DS5565-A-E312) is still ongoing when the above condition is met, the sponsor intends to take a snapshot of the database of this open-label extension study to support registration. The totality of the study data for DS-5565-A-E312 will be analyzed at the conclusion of the study.

11.9. Data and Safety Monitoring Board

An independent DSMB will be responsible for providing independent recommendations to the sponsor about evolving risk-benefit observed in the course of the double-blind preceding studies and this open-label extension study. The DSMB will review safety data in an ongoing manner to monitor and assure overall safety of the study subjects. In accordance with an agreed-upon charter, the DSMB will meet periodically, on a regular and/or ad hoc basis, to discuss and address any emerging safety or tolerability issues, including SAEs, discontinuations due to AEs, etc., as well as other relevant study information, such as recruitment status, ineligibility rates, and data quality. Based on any formal DSMB review meeting where 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 the ICF
- Suspend the study (or a cohort) until further notice, with recommendations for further action to address specific issues and appropriately managing active study subjects
- Terminate the study (or a cohort) with provisions for orderly discontinuation in accordance with GCP.

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

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

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

The sponsor (Head of Clinical Safety and Pharmacovigilance) 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. This adjudication will be independent of the investigators. The HAC will complete assessments on an ongoing basis. Adjudication of hepatic events will be based on evaluation of eCRFs and source documents, as available, including but not limited to hospital discharge summaries, diagnostic imaging, histopathology, consultation, and laboratory reports.

11.11. Sample Size Determination

Subjects who complete the double-blind studies are eligible to rollover to this open-label extension study. Although it's unknown how many subjects will complete the double-blind studies, the number is anticipated to be between 2100 and 2500. In addition subjects who did not participate in a preceding double-blind study (referred to as de novo subjects) may be enrolled. Overall, the goal of the open-label extension study is to collect long-term safety data on approximately 500 subjects exposed to DS-5565 for at least 52 weeks. During the conduct of the open-label study, subject withdrawal rates will be closely monitored. Entry into the open-label study will be stopped when the sponsor anticipates that the desired number of subjects completing 52 weeks can be achieved.

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 (e.g. eCRFs, source data, and other pertinent documents).

The monitor is responsible for visiting site(s) at regular intervals throughout the study according to the clinical monitoring plan 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 eCRFs 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 eCRFs.

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.

By signing this protocol, the investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed and documented.

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

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 enrolled, 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.

Subjects will be provided with an electronic device to capture their daily pain intensity rating, sleep interference score. The data from these diaries will be integrated into the eCRF. Questionnaires will be administered via electronic devices at each site visit, and data collected on these devices will be integrated into the eCRF.

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 SID.

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.

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

All medical history (except terms pre-specified on the eCRF) 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 eCRF will be included on the Signature List.

Source documents are original documents, data, and records from which the subject's eCRF 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 the following:

- Subject files containing completed informed consents and supporting copies of source documentation (if kept).
- Study files containing the protocol with all amendments, Investigator 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 eCRFs 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, eCRFs, inventory of study product, regulatory documents (e.g. 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

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/IEC, and where relevant by the regulatory authorities, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB/IEC 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.

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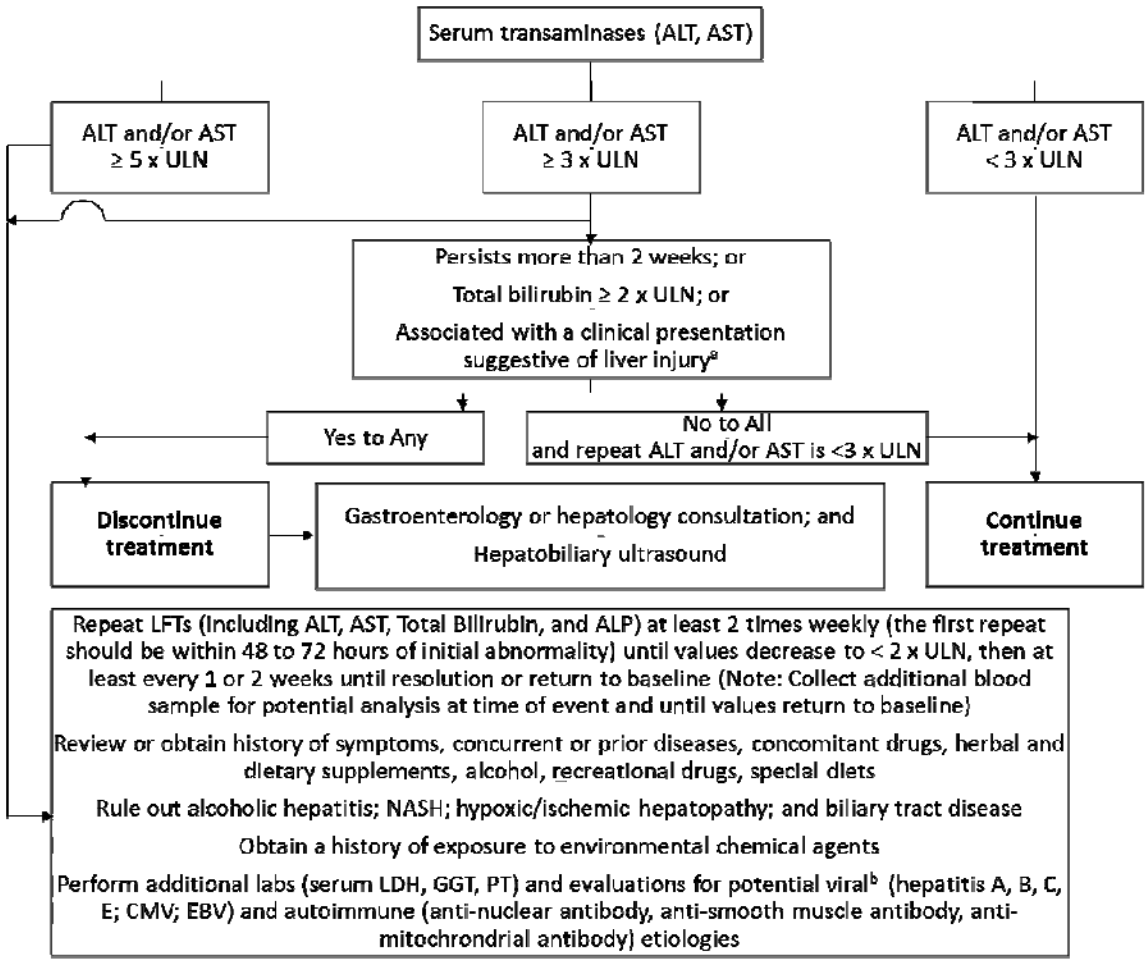
17. APPENDICES

17.1. Aminotransferase Elevations: Monitoring and Treatment Discontinuation

Figure 17.1: Aminotransferase Elevations: Monitoring and Treatment Discontinuation



[a] i.e. including the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia

[b] Evaluations for potential viral etiologies will include: Hep A Ab by IgM acute, HBsAg, HBeAg, anti-HBc, Hep C Ab, Hep C RNA by PCR, Hep E IgG Ab, Hep E IgM Ab, EBV IgG Ab, EBV IgM Ab, and CMV DNA by PCR

Abbreviations: ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase; CMV = cytomegalovirus, EBV = Epstein-Barr virus, GGT = gamma-glutamyltransferase, LDH = lactate dehydrogenase, LFT = liver function test, PT = prothrombin time, ULN = upper limit of normal

17.2. Cockcroft-Gault Equation

The estimated CrCl rate (mL/min) will be calculated using the Cockcroft-Gault equation based on actual weight in kilograms (1 kilogram = 2.2 pounds):

Conventional – serum creatinine in mg/dL:

Male:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in mg/dL)} \times 72}$$

Female:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in mg/dL)} \times 72} \times 0.85$$

International System of Units (SI) – serum creatinine in µmol/L:

Male:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in } \mu\text{mol/L)} \times 72 \times 0.0113}$$

Female:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in } \mu\text{mol/L)} \times 72 \times 0.0113} \times 0.85$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.

17.3. Schedule of Events

Table 17.1: Schedule of Events

Study Period	**Screening/Baseline (De Novo Only)**			**Start of Tx**	**on-Treatment**				**End of Tx/Et**	**Follow-Up[a]**		
Visit	**1**	**2**	**3**	**4**	**5**	**6-11**	**12**	**13-20**	**21**	**22**	**23**	**24**
Telephone Contact	--	**X**	--	--	--	--	--	--	--	**X**		**X**
Week	**-3**	**-2**	**-1**	**0**	**1**	**3, 5, 7, 9, 11, 13**	**16**	**20, 24, 28, 32, 36, 40, 44, 48**	**52**	**52.5**	**54**	**56**
Visit Window (Days)	--	--	--	--	**±3**	**±3**	**±3**	**±7**	**±7**	**±1**	**±3**	**±7**
Informed consent	DN			X[b]								
Inclusion/exclusion	DN			X								
Demographic information	DN			X[b]								
Medical/surgical history	DN			X[b]								
Adverse event reporting		DN	DN	X[c]	X	X	X	X	X	X	X	X
Washout instructions		DN										
Concomitant medications	DN	DN	DN	X[c]	X	X	X	X	X	X	X	X
Vital signs	DN			X[d]	X	X	X	X	X		X	
Height	DN			X[b]								
Weight	DN			X[d]	X	X	X	X	X		X	
Physical examination[e]	DN			X	X	X	X	X	X			
Fundoscopy[e]	DN							DN (V.14)	DN			
C-SSRS	DN			X[d]	X	X	X	X	X		X	
WPI/SSS	DN											

Study Period	**Screening/Baseline (De Novo Only)**			**Start of Tx**	**on-Treatment**				**End of Tx/Et**	**Follow-Up**[a]		
Visit	**1**	**2**	**3**	**4**	**5**	**6-11**	**12**	**13-20**	**21**	**22**	**23**	**24**
Telephone Contact	--	**X**	--	--	--	--	--	--	--	**X**		**X**
Week	**-3**	**-2**	**-1**	**0**	**1**	**3, 5, 7, 9, 11, 13**	**16**	**20, 24, 28, 32, 36, 40, 44, 48**	**52**	**52.5**	**54**	**56**
Visit Window (Days)	--	--	--	--	**±3**	**±3**	**±3**	**±7**	**±7**	**±1**	**±3**	**±7**
M.I.N.I	DN											
12-lead electrocardiogram	DN			X					X			
Clinical laboratory tests	DN			X[d]	X	X	X	X	X			
Pregnancy test[f]	DN			X[d]	X	X	X	X	X		X	

Table 17.1: Schedule of Events (Continued)

Study Period	**Screening/Baseline (De Novo Only)**			**Start of Tx**	**on-Treatment**				**End of Tx/Et**	**Follow-Up[a]**		
Visit	**1**	**2**	**3**	**4**	**5**	**6-11**	**12**	**13-20**	**21**	**22**	**23**	**24**
Telephone Contact	--	**X**	--	--	--	--	--	--	--	**X**		**X**
Week	**-3**	**-2**	**-1**	**0**	**1**	**3, 5, 7, 9, 11, 13**	**16**	**20, 24, 28, 32, 36, 40, 44, 48**	**52**	**52.5**	**54**	**56**
Visit Window (Days)	--	--	--	--	**±3**	**±3**	**±3**	**±7**	**±7**	**±1**	**±3**	**±7**
PWC										X	X	
Study drug compliance					X	X	X	X	X			
Contact IXRS	DN			X	X	X	X	X	X			
Study drug dispensing[g]				X	X	X	X	X[h]				
PGIC									X			
HADS				X					X			
EQ-5D and SF-36				X					X			
Provide daily diary			DN									
Review/collect daily diary				X[i]		X[i]		X[i]	X[i]			
Pain intensity rating				X[i]		X[i]		X[i]	X[i]			
Sleep interference score				X[i]		X[i]		X[i]	X[i]			

DN denotes visits and assessments for de novo subjects only.

a: The follow-up period will comprise a telephone contact 3 days after the last dose, a clinic visit at 2 weeks after the last dose (Week 54 if the subject completes treatment), and a telephone contact at 4 weeks after the subject's last dose of study treatment (Week 56 if the subject completes treatment).

b: For rollover subjects, informed consent will be obtained before the start of the End-of-Tapering visit in the preceding study and demography, height, and medical history will be used from the preceding study and will not be repeated. For de novo subjects, these assessments are not applicable at Visit 4.

c: For rollover subjects, any ongoing adverse events and concomitant medications should be recorded from the preceding study

d: For rollover subjects, values for vital signs, weight, C-SSRS, clinical safety laboratory tests, and pregnancy test will be taken from the End-of-Tapering visit of the preceding study and hence will not be repeated.

e: A full physical examination will be performed at Visit 1 (for de novo subjects) or Visit 4 (for rollover subjects) and at Visit 21 (for all subjects). An abbreviated physical examination will be performed at Visits 5 to 20. Refer to Section 9.9.2 for details. Fundoscopy (for de novo subjects) will be performed at Visit 1 (with pupil dilation) or a scanning laser ophthalmoscopy examination, Visit 14 (without pupil dilation) or a scanning laser ophthalmoscopy examination, and Visit 21 (with pupil dilation) or a scanning laser ophthalmoscopy examination.

f: A serum pregnancy test will also be performed for all women at all clinic visits (except as noted in footnote d) through the End-of-Treatment/Early Termination visit. A urine pregnancy test will be performed for all WOCBP at the Follow-up clinic visit.

g: Subjects receiving 15 mg QD will be dispensed a 1-month supply (1 card). Subjects receiving 15 mg BID can be dispensed every 2 weeks (1 card) or monthly (2 cards).

h: At Visit 20 (Week 48), subjects should be instructed to take all study medication, as scheduled, up until the day of their End-of-Treatment visit (Visit 21, Week 52), but not on the morning of Visit 21 (i.e. subjects should complete dosing on the evening prior to their End-of-Treatment visit).

i: For rollover subjects, pain and sleep interference scores from the End-of-Tapering visit in the preceding study will be used as the baseline values for this study. In this study, the pain and sleep interference scores will be recorded during the 7 days prior to Visit 11 (Week 13), Visit 14 (Week 24), Visit 17 (Week 36), Visit 20 (Week 48), and Visit 21 (Week 52). For de novo subjects only, pain diary scores will be recorded during the 7 days prior to Visit 4 (Start-of-Treatment). During the 7 days prior to these visits, every day upon awakening, prior to taking study medication, the subject should indicate the number that best describes his or her worst pain over the previous 24 hours and complete the sleep interference question.

Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale, DN = de novo, ET = early termination, IXRS = interactive voice/web response system, PGIC = Patient Global Impression of Change, PWC = Physician Withdrawal Checklist, HADS = Hospital Anxiety and Depression Scale, EQ-5D = EuroQoL Instrument 5 Domains, SF-36 = Short Form 36, Tx = treatment, WOCBP = women of child-bearing potential, SSS = Symptom Severity Scale, WPI = Widespread Pain.