CLINICAL STUDY PROTOCOL

AN ASIAN, PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED 14-WEEK STUDY OF DS-5565 IN PATIENTS WITH DIABETIC PERIPHERAL NEUROPATHIC PAIN FOLLOWED BY A 52-WEEK OPEN-LABEL EXTENSION

-For Double-Blind Study-

DS5565-A-J303

VERSION 6.0, 18 Apr 2016

DAIICHI SANKYO

IMPORTANT STUDY ADMINISTRATIVE INFORMATION

Sponsor	Daiichi Sankyo Co., Ltd. 3-5-1, Nihonbashi-honcho, Chuo-ku, Tokyo 103-8426, Japan TEL: see Section 15.10.1 FAX: see Section 15.10.1
Contract Research Organization (Japan):	CMIC Co., Ltd. 1-1-1, Shibaura, Minato-ku, Tokyo, 105-0023, Japan PPD PPD
Contract Research Organization (Korea):	Quintiles Transnational Korea Co., Ltd. 13th Floor, World Tower Building, 558 Songpa-daero, Songpa-gu, Seoul, Korea 138-731 PPD PPD
Contract Research Organization (Taiwan):	Quintiles Taiwan Ltd. 8F, No. 134, Sec. 3, Min Sheng East Road, Taipei, 105, Taiwan, R.O.C. PPD PPD
Contract Research Organization (Malaysia):	Quintiles Malaysia Sdn. Bhd. Suite D-08-02 Plaza Mont Kiara, No. 2 Jalan Kiara, Mont Kiara, 50480 Kuala Lumpur, MALAYSIA PPD PPD

INVESTIGATOR AGREEMENT

AN ASIAN, PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED 14-WEEK STUDY OF DS-5565 IN PATIENTS WITH DIABETIC PERIPHERAL NEUROPATHIC PAIN FOLLOWED BY A 52-WEEK OPEN-LABEL EXTENSION

Sponsor Approval:

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

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

Investigator's Signature:

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

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

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

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

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

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

PROTOCOL SYNOPSIS

Protocol Number:	DS5565-A-J303
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 Asian, phase 3, multicenter, randomized, double-blind, placebo-controlled 14-week study of DS-5565 in patients with diabetic peripheral neuropathic pain (DPNP) followed by a 52-week open-label extension
Study Phase:	Phase 3
Indication Under Investigation:	DPNP
Study Objectives:	Primary objective: To compare change in the Average Daily Pain Score (ADPS) from baseline to Week 14 in Asian subjects with DPNP receiving 10 mg BID and 15 mg BID of DS-5565 versus placebo Secondary objectives: • To compare change in the ADPS from baseline to Week 14 in Asian subjects with DPNP receiving 15 mg QD of DS-5565 versus placebo • To compare the ADPS responder rate (proportion of subjects with ≥ 30%, and ≥ 50% reduction from baseline to Week 14) between each arm of DS-5565 and placebo • To evaluate the effect of DS-5565 on additional pain questionnaires, including the Short-Form McGill Pain Questionnaire ([SF-MPQ]: sensory, affective and total subscales, Visual Analog Scale [VAS], and present pain intensity) and the modified Brief Pain Inventory (Short Form) ([BPI-SF]: pain intensity, functionality, and impact of pain) • To assess the effect of DS-5565 on quality of life (QOL), mood and sleep, patient impressions in pain, and symptoms • To collect blood samples for pharmacokinetic analyses • To characterize the safety and tolerability of DS-5565, based on the incidence of adverse events (AEs), discontinuations due to AEs, changes in physical findings, and results of safety monitoring
Study Design:	Multinational, randomized, double-blind, placebo-controlled, parallel-group study The total study duration will be approximately 16 weeks,

	consisting of 1-week observation period, 14-week treatment period and 1-week follow-up period after last dose. After completion of the observation period, the eligible subjects will be randomized into one of 4 arms, placebo, DS-5565 15 mg QD, DS-5565 10 mg BID, or DS-5565 15 mg BID at the ratio of 2:1:1:1, respectively. The titration period will be applied at the first week of 10 mg BID, and at the first 2 weeks of 15 mg QD and 15 mg BID. After the titration period, the drug will be administered for 12 or 13 weeks at the assigned dose. Any subjects who have been taking prohibited concomitant drugs will undergo a washout period of 7 days or more, prior to the screening.
Study Duration (from FPI to LPLV):	Study duration: January 2015 to May 2017
Study Sites and Location:	Approximately 200 study sites in Japan, Korea, Taiwan and Malaysia
Planned Sample Size:	Approximately 750 subjects will be randomized in the study.
Subject Eligibility Criteria:	Inclusion Criteria: Subjects must satisfy all of the following criteria to be included in the study. 1) Age ≥ 20 years at informed consent 2) Able to give written informed consent for study participation, understand procedures of this study, and complete patient-reported questionnaires adequately 3) Type 1 or type 2 diabetes mellitus at screening 4) Painful distal symmetric polyneuropathy, diagnosed at least 6 months prior to screening (see Procedures manual for the Diagnosis of Diabetic Peripheral Neuropathy and Neurological Examination for details) 5) At screening, a pain scale of ≥ 40 mm on VAS of SF-MPQ 6) At randomization, a pain scale of ≥ 40 mm on VAS of SF-MPQ, and completion of at least 4 days of daily pain diaries with an ADPS of ≥ 4 over the past 7 days on the 11-point Numerical Rating Scale (NRS) Exclusion Criteria: Subjects who meet any of the following criteria will be excluded from participation in the study. 1) At screening, a pain scale of ≥ 90 mm on VAS of SF-MPQ 2) At randomization, a pain scale of ≥ 90 mm on VAS of SF-MPQ, or at least a daily pain score of ≥ 9 during observation period 3) HbA1c (National Glycohemoglobin Standardization Program) > 10.0% at screening

	4) Uncontrolled blood glucose at screening or randomization that may require changes in diabetes treatment (non-insulin drug therapy, exercise therapy, diet therapy) during study 5) Other severe pain at screening or randomization, unrelated to diabetic peripheral neuropathy (DPN), that may confound the assessment of DPNP 6) Neurologic disorders at screening or randomization, unrelated to DPN, that may confound the assessment of DPNP 7) Major psychiatric disorders at screening or randomization 8) Amputation of lower limb parts, other than toes, prior to screening or randomization 9) Use of prohibited concomitant drugs within 7 days or change of restricted concomitant drugs within 30 days prior to screening 10) Skin conditions that could confound the assessment of DPNP 11) Previous administration of pregabalin ≥ 300 mg/day or gabapentin ≥ 1200 mg/day, declared lack of effect 12) Creatinine clearance (using the Cockcroft-Gault equation) < 60 mL/min at screening 13) Malignancy other than basal cell carcinoma within the past 2 years prior to screening 14) Clinically significant unstable neurologic, ophthalmologic, hepatobiliary, respiratory, hematologic illness or unstable cardiovascular disease (eg, severe hypotension, uncontrolled cardiac arrhythmia, or myocardial infarction) within 12 months prior to screening 15) Clinically significant findings on electrocardiogram (ECG) at screening 16) History of pernicious anemia, untreated hypothyroidism, or human immunodeficiency virus infection 17) Known history of positive Hepatitis B antigen or Hepatitis C antibody 18) Pregnancy, potential pregnancy, breast feeding, or subject unwilling to take reliable contraceptive measures during the study or for 4 weeks after study completion 19) Known hypersensitivity to pregabalin or gabapentin 20) Participation in another clinical study, either currently or within 30 days prior to providing of informed consent 21) Experience of participating DS-5565 clinical study and receiving investigational product 22) Abuse of illicit drugs or alcohol within one year prior to

	screening 23) Response of "yes" to any of the questions on the Columbia-Suicide Severity Rating Scale (C-SSRS) at screening or randomization in relation to events occurring within the past 12 months 24) Previous treatment with drugs that could cause irreversible retinal degeneration 25) At screening, clinical laboratory values exceeding limits listed in Table 4-1 (see Section 4.1.3) 26) The subject who is considered inappropriate for the study at the discretion of the investigator or sub-investigator 27) Response of "yes" to the suicidality question (current or past) on the Major Depressive Episode Module (Module A) or response of "yes" to any question of B1b, B3 through B11c, B13, or B14 in the Suicidality Module (Module B) on the Mini-international Neuropsychiatric Interview (MINI) Interview (Version 6.0) at screening
Dosage Form, Dose, and Route of Administration:	For the fixed-dose period, DS-5565 at a total daily dose of 15 mg (15 mg QD), 20 mg (10 mg BID) and 30 mg (15 mg BID), formulated in 5 mg, 10 mg and 15 mg tablets, OR matching placebo will be administered orally, twice daily (in the morning and at bedtime). For the titration period, DS-5565 will be administered with 10 mg (5 mg BID) during the first week for 10 mg BID and 15 mg BID treatment group, and followed by 20 mg (10 mg BID) during the second week for 15 mg BID treatment group. For 15 mg QD treatment group, DS-5565 will be administered with 5 mg (5 mg QD) during the first week and followed by 10 mg (10 mg QD) during the second week.
Study Endpoints:	Primary endpoint: • Change in ADPS from baseline to Week 14, rating averaged daily pain score over a 7-day period, based on entries in patients' daily pain diaries Secondary endpoints • ADPS Responder rate defined as the proportion of subjects with ≥ 30%, and ≥ 50% reduction from baseline to Week 14 • Change from baseline in parameters assessed using SF-MPQ • Change from baseline in parameters assessed using the modified BPI-SF (measurements of pain intensity, functionality, and impact of pain) • Patient Global Impression of Change (PGIC)

	• Change from baseline in average daily sleep-interference score (ADSIS) • Change from baseline in Medical Outcomes Study (MOS) sleep scale • Change from baseline in the Hospital Anxiety and Depression Scale (HADS) • Changes from baseline in QOL, using the SF-36 • Evaluation of Symptoms
Statistical Analyses:	The modified intent-to-treat (mITT) analysis set will be used as a primary analysis set for all efficacy analyses. Observed ADPS and change from baseline will be summarized by treatment and week (including Week 14/last observation carried forward [LOCF] and Week 14/baseline observation carried forward [BOCF]). Mean change from baseline in ADPS will be compared between each DS-5565 arm and placebo at Week 14 using the following multiple imputation (MI) method and mixed-effect model for repeated measurements (MMRM). The primary imputation will be based on "nonfuture dependence" model [29 - 31] using the pattern mixture approach with shifting parameters under the missing not at random (MNAR) mechanism for the missing weekly ADPS data. Reason for dropout together with the time of dropout will be used for constructing the missing data pattern. The statistical model used for the MI data generation will be the Markov Chain Monte Carlo (MCMC) method with adjustment for covariates (eg, treatment group, age, sex) to produce a monotone pattern first, and then the imputation will continue using the Regression with Predictive Mean Matching (REGPMM) method for the monotone pattern with the same set of covariates. Each complete imputed dataset will be analyzed using the MMRM with treatment, week, treatment-by-week as the fixed effects, week as the repeated measure, and baseline ADPS as the covariate. The results of MMRM analysis from each complete imputed dataset will be combined using Rubin's rule. All reasons for discontinuation will be categorized, to the extent possible, into either lack of efficacy (LOE) or adverse event (AE) based on detail specified in the Case Report Form. Only reasons that cannot be classified into the above two categories will be considered as "all other reasons (AOR)" The primary shifting parameter values

	corresponding to the three categories in the pattern mixture model (PMM) will be chosen as (1.0, 1.0, 0.5) for dropouts due to AE, LOE and AOR, respectively, and the corresponding shifting amount of the weekly ADPS imputed at first missing week is given by (1.0, 1.0, 0.5)*RSD*U(0,1) where U(0,1) is a random variable from a uniform distribution with a range of 0 to 1, and RSD is the residual standard deviation at first missing week after imputation. The type I error rate will be controlled at less than 0.05 for the multiple comparisons of the primary efficacy analyses using combination approach of Bonferroni-Holm method and gate-keeping procedure (See Section 11.5.1 for detail). Sensitivity analyses will include following: • The above primary "nonfuture dependence" MNAR model with different shift parameters including (0, 0, 0) • Placebo multiple imputation[27,28] • MMRM using observed data only • Analysis of covariance (ANCOVA) using BOCF • ANCOVA using LOCF • The above primary "nonfuture dependence" MNAR model with the same shift parameters as the primary analysis (i.e., (1.0, 1.0., 0.5) using per-protocol set [PPS]) Response rate, defined as the proportion of subjects with ≥ 30%, and ≥ 50% reduction from baseline in ADPS, will be compared between each DS-5565 arm and placebo, using logistic regression model. The cumulative distribution for reduction from baseline in ADPS will be provided as a continuous responder analysis[25]. For the safety endpoints, AEs, clinical laboratory test results, vital signs (including body weight), ECG, physical findings, C-SSRS, and HADS will be summarized for the safety analysis set.

TABLE OF CONTENTS

IMPORTANT STUDY ADMINISTRATIVE INFORMATION 2
INVESTIGATOR AGREEMENT 3
PROTOCOL SYNOPSIS 4
TABLE OF CONTENTS 10
LIST OF IN-TEXT TABLES 16
LIST OF ABBREVIATIONS 17
1. INTRODUCTION AND BACKGROUND INFORMATION 20
1.1 Data Summary 20
1.1.1 Investigational Product(s) 20
1.1.1.1 Name 20
1.1.1.2 Description 20
1.1.1.3 Intended Use Under Investigation 20
1.1.1.4 Nonclinical Studies 20
1.1.1.5 Clinical Experience 20
1.2 Study Rationale 22
1.3 Risks and Benefits for Study Subjects 23
2. STUDY OBJECTIVES AND HYPOTHESES 24
2.1 Study Objectives 24
2.1.1 Primary Objective 24
2.1.2 Secondary Objectives 24
2.2 Study Hypothesis 24
3. STUDY DESIGN 25
3.1 Overall Plan 25
3.1.1 Study Type 25
3.1.2 Study Scheme 25
3.1.3 Study Endpoints 26
3.1.3.1 Primary Endpoint 26
3.1.3.2 Secondary Endpoints 26
3.1.4 Duration of Subject Participation 27
3.2 Discussion of Study Design 27
3.2.1 Dosage of DS-5565 27
3.2.2 Duration of Study Treatment 28
3.2.3 Control Treatment 28
3.2.4 Study Endpoints 28

4. STUDY POPULATION 29
4.1 Enrollment 29
4.1.1 Procedures for Subject Enrollment 29
4.1.2 Inclusion Criteria 29
4.1.3 Exclusion Criteria 30
4.2 Subject Withdrawal 33
4.2.1 Withdrawal Criteria 33
4.2.2 Reasons for Withdrawal 33
4.2.3 Withdrawal Procedures 34
4.2.4 Stopping Rules for the Study 35
5. TREATMENT ADMINISTERED 36
5.1 Investigational Products 36
5.1.1 Study Treatments 36
5.1.1.1 Investigational Product 36
5.1.1.2 Investigational Product Placebo 36
5.1.2 Dosing Regimens for the Study 36
5.1.3 Method of Assigning Subjects to Treatments and Blinding 37
5.1.3.1 Method of Assigning the Investigational Product to Subjects 37
5.1.3.2 Blinding 37
5.1.3.3 Preparation and Management of Emergency Codes 38
5.1.3.4 Procedures for Emergency Unblinding 38
5.1.3.5 Subject Replacement 40
5.1.4 Method of Assessing Treatment Compliance 40
5.1.5 Labeling and Packaging 40
5.1.6 Storage 42
5.1.7 Drug Accountability 42
5.2 Concomitant Medications and Treatments 42
5.2.1 Prohibited Concomitant Medications 42
5.2.2 Restricted Concomitant Medications 44
5.2.3 Rescue Medications 44
5.2.4 Prohibited Concomitant Therapies 44
5.2.5 Other 44
6. STUDY PROCEDURES 45
6.1 Screening (Visit 1, 7 days prior to randomization) 45
6.2 Randomization (Visit 2, Day 1) 46

6.3 Treatment Period 46
6.3.1 Visit 3 and Visit 4 46
6.3.2 Visit 5, Visit 6, Visit 7, Visit 8, and Visit 9 47
6.4 End of Treatment/Early Termination (Visit 10) 48
6.5 Post-treatment Follow-up (Visit 11, 7 days after the completion of administration) 49
7. EFFICACY ASSESSMENTS 50
7.1 Primary Efficacy Variable(s) 50
7.2 Secondary Efficacy Variable(s) 50
8. PHARMACOKINETIC AND BIOMARKER ASSESSMENTS 54
8.1 Pharmacokinetic Variable(s) 54
8.2 Biomarker Variable(s) 54
9. SAFETY ASSESSMENTS 55
9.1 Adverse Events 55
9.1.1 Definition of Adverse Event 55
9.1.2 Items to Be Investigated Concerning Adverse Events 56
9.1.3 Definition of Adverse Drug Reaction 58
9.1.4 Actions to Be Taken When Adverse Events Occur 58
9.2 Actions to Be Taken When Serious Adverse Events Occur 59
9.3 Exposure In Utero During Clinical Studies 59
9.4 Clinical Laboratory Evaluations 60
9.5 Vital Signs 64
9.6 Electrocardiograms 64
9.7 Physical Findings 64
9.7.1 Body Height and Weight 64
9.7.2 Physical Examinations 64
9.7.3 Evaluation of Edema 64
9.8 Other Safety Assessments 65
9.8.1 Neurological Examination 65
9.8.2 Ophthalmologic Examination 65
9.8.3 Columbia-Suicide Severity Rating Scale[14] 65
9.8.4 Hospital Anxiety and Depression Scale[12] 66
9.8.5 Pregnancy test 66
10. OTHER ASSESSMENTS 67
11. STATISTICAL METHODS 68
11.1 Objective 68

11.2 General Statistical Considerations 68
11.3 Analysis Sets 69
11.4 Study Population Data 69
11.5 Efficacy Analyses 69
11.5.1 Primary Efficacy Analyses 69
11.5.2 Secondary Efficacy Analyses 71
11.5.2.1 Responder Rate for Averaged Daily Pain Score 71
11.5.2.2 Short-Form McGill Pain Questionnaire 71
11.5.2.3 Modified Brief Pain Inventory (Short Form) 72
11.5.2.4 Patient Global Impression of Change 72
11.5.2.5 Sleep-Interference Score 72
11.5.2.6 Medical Outcomes Study Sleep Scale 72
11.5.2.7 Hospital Anxiety and Depression Scale 72
11.5.2.8 SF-36 72
11.5.2.9 Evaluation of Symptoms 73
11.6 Pharmacokinetic/Biomarker Analyses 73
11.6.1 Pharmacokinetic Analyses 73
11.6.2 Biomarker Analyses 73
11.7 Safety Analyses 73
11.7.1 Adverse Event Analyses 73
11.7.2 Clinical Laboratory Evaluation Analyses 74
11.7.3 Vital Sign Analyses 74
11.7.4 Electrocardiogram Analyses 74
11.7.5 Physical Finding Analyses 74
11.7.6 Columbia-Suicide Severity Rating Scale 75
11.7.7 Hospital Anxiety and Depression Scale 75
11.7.8 Other Safety Analyses 75
11.8 Other Analyses 75
11.9 Data Safety Monitoring Board 75
11.10 Hepatic Adjudication Committee 76
11.11 Sample Size Determination 76
12. DATA INTEGRITY AND QUALITY ASSURANCE 78
12.1 Monitoring and Inspections 78
12.2 Data Collection 79
12.2.1 Style of Data Collection 79

12.2.1.1 Case Report Form 79
12.2.1.2 Electronic Daily Diary 79
12.2.1.3 Other Reports 80
12.2.2 Preparation of Case Report Forms and Daily Diaries 80
12.2.3 Signatures or Seals on the Case Report Form 80
12.2.4 Data Correction 80
12.3 Data Management 81
12.4 Study Documentation and Storage 81
12.4.1 Definition of Source Documents 81
12.4.2 Storage 82
12.5 Record Keeping 82
13. FINANCING AND INSURANCE 83
13.1 Finances 83
13.2 Reimbursement, Indemnity, and Insurance 83
14. PUBLICATION POLICY 84
15. STUDY ADMINISTRATIVE INFORMATION 85
15.1 Compliance Statement, Ethics, and Regulatory Compliance 85
15.2 Subject Confidentiality 85
15.3 Informed Consent Procedures 85
15.4 Regulatory Compliance 86
15.5 Protocol Deviations 87
15.6 Supply of New Information Affecting the Conduct of the Study 87
15.7 Duration of the Study 87
15.8 Protocol Amendments 88
15.9 Study Discontinuation or Suspension 88
15.10 Organization 89
15.10.1 Sponsor 89
15.10.1.1 Sponsor's Responsible Medical Expert 89
15.10.1.2 Sponsor's Responsible Medical Adviser 89
15.10.1.3 Sponsor's Clinical Study Lead 89
15.10.1.4 Sponsor's Delivery Lead 89
15.10.2 Academic Research Organization 90
15.10.3 Coordinating Investigator 90
15.10.3.1 Coordinating Investigator in Japan 90
15.10.3.2 Coordinating Investigator in Korea 90

15.10.3.3 Coordinating Investigator in Taiwan 90
15.10.4 Contract Research Organization 90
15.10.4.1 Contract Research Organization in Charge of Monitoring in Japan 90
15.10.4.2 Contract Research Organization in Charge of Monitoring in Korea 91
15.10.4.3 Contract Research Organization in Charge of Monitoring in Taiwan..... 91
15.10.4.4 Contract Research Organization in Charge of Monitoring in Malaysia..... 91
15.10.4.5 Contract Research Organization in Charge of Interactive Web Response System91
15.10.4.6 Contract Research Organization in Charge of Emergency Contact 91
15.10.4.7 Randomization manager 92
15.10.5 Central Laboratory 92
15.10.5.1 Bioanalytical Laboratory 92
15.10.5.2 Central Laboratory Management 92
15.10.5.3 Central Laboratory in Japan..... 92
15.10.5.4 Central Laboratory Management in Korea 92
15.10.5.5 Central Laboratory in Korea 93
15.10.5.6 Central Laboratory in Taiwan 93
15.10.5.7 Central Laboratory in Singapore..... 93
15.10.6 Data Safety Monitoring Board..... 93
15.10.7 Contract Research Organization in Charge of Data Safety Monitoring Board Coordination..... 94
15.10.8 Hepatic Adjudication Committee..... 94
15.10.9 Contract Research Organization in Charge of Hepatic Adjudication Committee Coordination..... 94
15.10.10 EDC System Development 95
15.10.11 EDC System Support 95
15.10.12 ePRO system Development and Support..... 95
16. REFERENCES 96
17. APPENDICES 98
17.1 Schedule of Events..... 98
17.2 Processing of Blood Samples for Pharmacokinetic Analyses..... 101

LIST OF IN-TEXT TABLES

Table 4-1 Hematology/Blood Chemistry Limits 32
Table 5-1 Method of Administration During the Treatment Period 37
Table 5-2 Drug Combinations During the Treatment Period (Week 1) 41
Table 5-3 Drug Combinations During the Treatment Period (Week 2) 41
Table 5-4 Drug Combinations During the Treatment Period (Week 3 to Week 14) 42
Table 9-1 Items to be Investigated for Adverse Event 57
Table 9-2 Laboratory Parameters to be Assessed, and Time of Assessment 61
Table 11-1 Statistical powers (%) of DS-5565 15 mg QD, 10 mg BID, and 15 mg BID being superior over placebo 77
Table 12-1 Electronic Data Capture System 79
Table 12-2 Electronic Patient Report Outcome System 79
Table 17-1 Study Visits 98
Table 17-2 Efficacy Assessment by Visit 100

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ADPS	Average Daily Pain Score
ADR	Adverse Drug Reaction
ADSIS	Average Daily Sleep Interference Score
AE	Adverse Event
A/G ratio	Albumin/Globulin ratio
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AMA	anti-mitochondrial antibody
ANA	anti-nuclear antibody
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ASMA	anti-smooth muscle antibody
AST	Aspartate Aminotransferase
BOCF	Baseline Observation Carried Forward
BPI-SF	Brief Pain Inventory (Short Form)
BUN	Blood Urea Nitrogen
CMV	Cytomegalovirus
CNS	Central Nervous System
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-Reactive Protein
C-SSRS	Columbia-Suicide Severity Rating Scale
DILI	Drug-Induced Liver Injury
DSMB	Data Safety Monitoring Board
DPN	Diabetic Peripheral Neuropathy
DPNP	Diabetic Peripheral Neuropathic Pain
EBV	Epstein-Barr Virus
eCRF	Electronic Case Report Form
EC	Independent Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
e-DISH	Evaluation of drug-induced serious hepatotoxicity
EIU	Exposure In Utero
EMA	European Medicines Agency
ePRO	Electronic Patient Report Outcome

ABBREVIATION	DEFINITION
FDA	Food Drug Administration
FM	Fibromyalgia
FPI	First Patient In
GCP	Good Clinical Practice (refers to ICH and CFR)
γ-GT(γ-GTP)	gamma-Glutamyl Transpeptidase
GOT	Glutamic Oxaloacetic Transaminase
GPT	Glutamic Pyruvic Transaminase
HAC	Hepatic Adjudication Committee
HADS	Hospital Anxiety and Depression Scale
ICF	Informed Consent Form
ICH	International Conference on Harmonization
INN	International Nonproprietary Names
IRB	Institutional Review Board
ISFLB	Independent Sub-Functional Lead of Biostatistics
IWRS	Interactive Web Response System
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LOCF	Last Observation Carried Forward
LOE	Lack of Efficacy
LPLV	Last Patient Last Visit
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MINI	Mini-international Neuropsychiatric Interview
mITT	Modified Intent-To-Treat
MMRM	Mixed-Effects Model for Repeated Measurements
MNAR	Missing Not At Random
MOS	Medical Outcomes Study
NASH	Nonalcoholic Steatohepatitis
NMDA	N-methyl-D-aspartate receptor
NRS	Numerical Rating Scale
PAP	PK Analysis Plan
PGIC	Patient Global Impression of Change
PHN	Post-Herpetic Neuralgia
PK	Pharmacokinetics
PMM	Pattern Mixture Model

ABBREVIATION	DEFINITION
PPS	Per-Protocol Set
PT	Prothrombin Time
QOL	Quality of Life
RBC	Red Blood Cell
REGPMM	Regression with Predictive Mean Matching
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SF-MPQ	Short-Form McGill Pain Questionnaire
TEAE	Treatment-Emergent Adverse Event
T-Bil	Total bilirubin
ULN	Upper Limit of Normal
VAS	Visual Analog Scale
WBC	White Blood Cell

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1 Data Summary

1.1.1 Investigational Product(s)

1.1.1.1 Name

DS-5565

1.1.1.2 Description

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

1.1.1.3 Intended Use Under Investigation

Diabetic peripheral neuropathic pain (DPNP)

1.1.1.4 Nonclinical Studies

Evidence from nonclinical studies suggests that neuropathic pain symptoms may be due to changes in the protein content of membranes of injured neurons ("membrane remodeling"). This process can lower the threshold for action potential generation, resulting in abnormal and spontaneous firing in peripheral and primary afferent and dorsal root ganglionic neurons. Treatment with an $\alpha_2\delta$ ligand is reported to reduce the calcium ion (Ca^{2+}) influx through voltage-dependent Ca^{2+} channels, and therefore to reduce the subsequent release of excitatory neurotransmitters such as glutamate, norepinephrine, and substance P.[1,2,3,4]

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

1.1.1.5 Clinical Experience

The efficacy, safety, and tolerability of DS-5565 were evaluated in 2 Phase 2 studies in subjects with DPNP in the US and Asia.

1.1.1.5.1 Phase 2 Study in the US

This was a randomized, double-blind, placebo- and active-controlled study in subjects

with DPNP in the US.

In this study, greater mean decreases from baseline to end-of-treatment (Week 5) in average daily pain score (ADPS) were observed in the DS-5565 treatment groups than in the placebo group. The mean changes from baseline to Week 5 (with last observation carried forward (LOCF) imputed for missing values) in ADPS were -2.0, -2.3, -2.7, -2.6, and -2.8 for the DS-5565 5 mg QD, 10 mg QD, 15 mg QD, 10 mg BID, and 15 mg BID treatment groups, respectively. By comparison, placebo and pregabalin showed mean changes of -1.9 and -1.8, respectively.

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

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

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

1.1.1.5.2 Phase 2 Study in Asia

This was a randomized, double-blind, placebo- and active-controlled study in subjects with DPNP in Asia.

The primary endpoint was the change from baseline in ADPS to Week 7 (with LOCF imputed for missing values). For the primary analysis, an ANCOVA was performed using treatment as the factor and baseline ADPS as the covariate to compare the mean change from baseline to Week 7/LOCF between each DS-5565 treatment group and placebo, between each DS-5565 treatment group and pregabalin, and between pregabalin and placebo. The mean changes from baseline to Week 7 (with LOCF imputed for missing values) in ADPS were -1.9, -1.8, and -1.7 for DS-5565 5 mg BID, 10 mg BID, and 15 mg BID treatment groups. By comparison, placebo and pregabalin showed mean changes of -1.5 and -1.4, respectively. The primary analysis was an ANCOVA on Week 7 LOCF data. The LS mean differences versus placebo in change in ADPS from baseline to Week 7 were -0.42, -0.37, and -0.30 for the DS-5565 5 mg BID, 10 mg BID, and 15 mg BID treatment groups, respectively. These LS mean differences were numerically lower than that in the placebo group, although the reduction was not statistically significant for any treatment groups.

All DS-5565 dose levels were generally well tolerated. Based on dose level, at least 1 TEAE was experienced by 48.9% of subjects in the DS-5565 5 mg BID group, 63.4% of subjects in the DS-5565 10 mg BID group, 73.3% of subjects in the DS-5565 15 mg BID group, 58.1% of subjects receiving pregabalin 150 mg BID, and 53.4% of subjects receiving placebo. The most common TEAEs (ie, those reported in ≥ 5% of subjects receiving DS-5565) experienced by subjects taking DS-5565 were: somnolence (14.7%), dizziness (11.0%), nasopharyngitis (8.4%).

1.2 Study Rationale

Currently available $\alpha_2\delta$ ligands, gabapentin and pregabalin, are established as effective first-line treatments for pain associated with diabetic peripheral neuropathy (DPN).[2,3] However, the dosage, and thus efficacy, of these agents is limited by frequent and significant CNS-related side effects, including dizziness and somnolence; associated weight gain and peripheral edema can also be problematic. As a result, a large proportion of patients with DPNP are left with insufficient pain relief, and new treatment options are needed.

DS-5565 is an oral analgesic drug being developed for DPNP and other indications. DS-5565 is an antagonist to the $\alpha_2\delta$ subunit of voltage-dependent Ca^{2+} channels, the main target molecule for the analgesic effect of pregabalin and gabapentin. Nonclinical (Section 1.1.1.4) and clinical (Section 1.1.1.5) data support the progress of DS-5565 into Phase 3 studies in DPNP to evaluate the effect of DS-5565 on ADPS as compared to placebo during the course of a 14 week (including titration period) double-blind treatment period.

1.3 Risks and Benefits for Study Subjects

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

Anticipated risks of DS-5565 include the occurrence of adverse reactions related to CNS depression, such as dizziness and somnolence, as well as peripheral edema. Other notable TEAEs that have been observed in Phase 1 and Phase 2 studies include elevations of hepatic transaminases and suicide. 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.

2. STUDY OBJECTIVES AND HYPOTHESES

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective is to compare change in the ADPS from baseline to Week 14 in Asian subjects with DPNP receiving 10 mg BID and 15 mg BID of DS-5565 versus placebo.

2.1.2 Secondary Objectives

- To compare change in the ADPS from baseline to Week 14 in Asian subjects with DPNP receiving 15mg QD of DS-5565 versus placebo
- To compare the ADPS responder rate (proportion of subjects with ≥ 30%, and ≥ 50% reduction from baseline to Week 14) between each arm of DS-5565 and placebo
- To evaluate the effect of DS-5565 on additional pain questionnaires, including the Short-Form McGill Pain Questionnaire ([SF-MPQ]: sensory, affective, and total subscales, Visual Analog Scale [VAS], and present pain intensity) and the modified Brief Pain Inventory (Short Form) ([BPI-SF]: pain intensity, functionality, and impact of pain)
- To assess the effect of DS-5565 on quality of life (QOL), mood and sleep, patient impressions in pain, and symptoms
- To collect blood samples for pharmacokinetic analyses
- To characterize the safety and tolerability of DS-5565, based on the incidence of adverse events (AEs), discontinuations due to AEs, changes in physical findings, and results of safety monitoring

2.2 Study Hypothesis

The primary hypothesis of this Phase 3 double-blind study is that at least one of the dose arm of DS-5565 10 mg BID and 15 mg BID will be superior to placebo in managing DPNP as measured by ADPS and will be generally well tolerated.

3. STUDY DESIGN

3.1 Overall Plan

3.1.1 Study Type

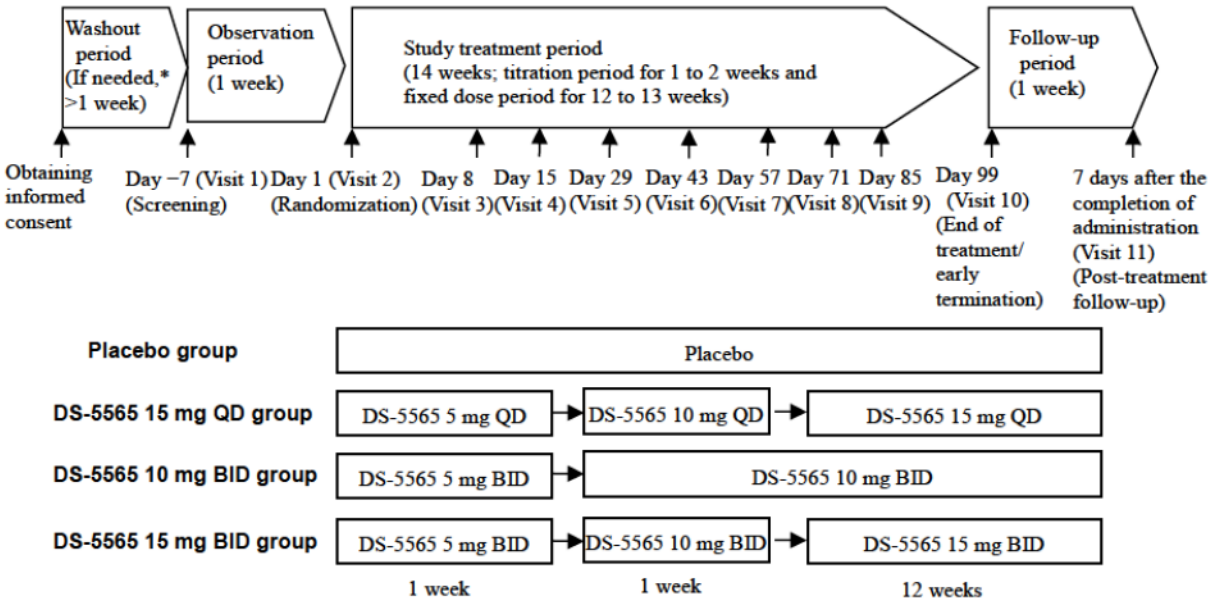
This is a multinational, randomized, double-blind, placebo-controlled, parallel-group study for treatment of DPNP.

Study sites: Approximately 200 study sites in Japan, Korea, Taiwan and Malaysia.
Planned sample size: Approximately 750 subjects will be randomized in the study.

3.1.2 Study Scheme

The total study duration (for an individual subject's participation) is approximately 16 weeks, consisting of an observation period (1 week), a titration period (1 to 2 weeks), a fixed-dose period (12 to 13 weeks), and a follow-up period (1 week) (See study scheme below).

If prohibited concomitant medications are used within 7 days prior to obtaining written informed consent, screening will follow a washout period of at least 7 days prior to screening. Informed consent must be obtained before initiating washout or screening. Enrollment will be limited to subjects who meet the inclusion/exclusion criteria described in Section 4.1.2 and 4.1.3. Subjects will be randomized to placebo or one of 3 different arms of DS-5565 (DS-5565 15 mg QD, 10 mg BID, or 15 mg BID) with randomization ratio of 2:1:1:1 in a double-blind fashion at randomization (Visit 2). Increasing the proportion of placebo arm is expected to minimize the placebo response by reducing the expectations of subjects assigned to active drug. After the completion of administration, subjects will be monitored for an additional follow-up observation period of 1 week. Follow-up observation is not required for subjects who are enrolled in an open-label extension study.
Further details of the study procedures are provided in the Schedule of Events (Section 17.1) and Study Procedures (Section 6).



* After informed consent is obtained, subjects who are under treatment with the prohibited concomitant medications (see 5.2.1) will undergo a washout period of 7 days or more.

3.1.3 Study Endpoints

3.1.3.1 Primary Endpoint

The primary efficacy endpoint is change in ADPS from baseline to Week 14, rating averaged daily pain score over a 7-day period, based on entries in patients' daily pain diaries.

3.1.3.2 Secondary Endpoints

- ADPS Responder rate defined as the proportion of subjects with ≥ 30%, and ≥ 50% reduction from baseline to Week 14
- Change from baseline in parameters assessed using SF-MPQ including 15 pain descriptors (ranked on a 4-stage intensity scale), the Present Pain Intensity index (ranked on a 6-stage intensity scale), and VAS (100-mm scale)
- Change from baseline in parameters assessed using the modified BPI-SF (measurements of pain intensity, functionality, and impact of pain, rated on an 11-point Numerical Rating Scale (NRS) [0 = no pain to 10 = worst possible pain])
- Patient Global Impression of Change (PGIC) assessed on a 7-point scale (from very much improved to very much worse)
- Change from baseline in average daily sleep-interference score (ADSIS)
- Change from baseline in Medical Outcomes Study (MOS) sleep scale including

average time to fall asleep, average sleep time per night, and the 5-point scales related to sleep disturbance
- Change from baseline in the Hospital Anxiety and Depression Scale (HADS) including 7 items to score depression (4-point scale) and 7 items to score anxiety (4-point scale)
- Changes from baseline in QOL, using the SF-36 including physical functioning, role-physical, social functioning, bodily pain, mental health, role-emotional, vitality, and general perception of health
- Evaluation of Symptoms, assessed on a 4-point scale

3.1.4 Duration of Subject Participation

The duration of subject participation will be approximately 16 weeks, including an observation period, a titration period, a fixed-dose period, and a follow-up period. No follow-up observation is required for subjects enrolled in an open-label extension study.

3.2 Discussion of Study Design

3.2.1 Dosage of DS-5565

It is expected that, in post-marketing, the dose of DS-5565 will be adjusted up or down depending on the patient's symptoms. Therefore, to identify multiple recommended clinical doses, the following 3 doses of DS-5565 were selected in the study for the fixed-dose period: 15 mg QD, 10 mg BID, and 15 mg BID. The doses were selected based on the results of the 2 Phase 2 studies of DS-5565 in patients with DPNP.

In the Asian Phase 2 study (DS5565-A-J202), DS-5565 showed numerically greater improvement in ADPS at doses of 5 mg BID, 10 mg BID, and 15 mg BID than placebo, although these differences versus placebo were not statistically significant. DS-5565 also showed statistically significant improvement in ADPS at doses of 15 mg QD, 10 mg BID, and 15 mg BID than placebo in the US Phase 2 study (DS5565-A-U201). In addition, the results for the secondary efficacy endpoints in the Asian Phase 2 study suggested a dose-dependent treatment effect of DS-5565. Safety analysis in the Asian Phase 2 study showed that DS-5565 was tolerated at doses of 5 mg BID, 10 mg BID, and 15 mg BID, although there were some AEs that should be monitored in future clinical studies of DS-5565.

On the basis of the results in the Asian Phase 2 study, 10 mg BID is expected to achieve a

good balance between efficacy and safety. In addition, 15 mg BID is expected to show a better efficacy profile than 10 mg BID, although 15 mg BID resulted in a somewhat higher incidence of TEAEs. The results in the US Phase 2 study suggested that 15 mg QD may be the minimum effective dose. However, the Asian Phase 2 study did not include the dose of 15 mg QD. Therefore, in this Asian Phase 3 study in patients with DPNP, 10 mg BID and 15 mg BID were selected as primary doses, and 15 mg QD as a secondary dose.

The dose of DS-5565 will be lower during the titration period than the fixed-dose period for subject safety.

3.2.2 Duration of Study Treatment

In the double-blind study, the efficacy of DS-5565 versus placebo in neuropathic pain will be evaluated. The European Medicines Agency (EMA) guideline[5] recommends that the treatment duration for fixed dose period be 12 weeks or longer. Therefore, the study will have 12 to 13 weeks of fixed-dose period. In addition, taking into consideration for subject safety, the study will have 1 to 2 weeks of titration period before the fixed-dose period. The dose of DS-5565 will be lower during the titration period than the fixed-dose period.

3.2.3 Control Treatment

Placebo will be used as the control treatment in the study. Inclusion of placebo is required in the EMA guideline[5].

3.2.4 Study Endpoints

In accordance with recommendations from the EMA guideline, the primary endpoint was selected as intergroup comparison of the amount of change in findings on an 11-point pain scale. Patients with neuropathic pain can experience seriously decreased QOL, not only from pain but also from factors such as poor sleep. To assess these factors, secondary endpoints were selected in areas such as sleep and QOL.

4. STUDY POPULATION

4.1 Enrollment

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

4.1.1 Procedures for Subject Enrollment

The investigator or sub-investigator will perform a mandatory interview to assess the eligibility of subjects for the study, after obtaining each subject's written informed consent, and will make necessary entries in the IWRS at screening. Any subjects who have been taking prohibited concomitant drugs will undergo a washout period of 7 days or more, prior to the observation period. After the screening visit (Visit 1), a 7-day observation period will be implemented before randomization.

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

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

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

4.1.2 Inclusion Criteria

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

1) Age ≥ 20 years at informed consent
2) Able to give written informed consent for study participation, understand procedures of this study, and complete patient-reported questionnaires adequately
3) Type 1 or type 2 diabetes mellitus at screening
4) Painful distal symmetric polyneuropathy, diagnosed at least 6 months prior to screening (see Procedures manual for the Diagnosis of Diabetic Peripheral

Neuropathy and Neurological Examination for details)

5) At screening, a pain scale of ≥ 40 mm on VAS of SF-MPQ
6) At randomization, a pain scale of ≥ 40 mm on VAS of SF-MPQ, and completion of at least 4 days of daily pain diaries with an ADPS of ≥ 4 over the past 7 days on the 11-point NRS

Rationale

1) Phase 1 and Phase 2 studies in elderly subjects showed no notable differences from the results obtained in non-elderly subjects with regard to safety, tolerability, and pharmacokinetics (PK). Thus, no upper limit was placed on age in this study. Because the PK and safety of this drug have not been established in children, and in order to obtain appropriate informed consent from the subjects themselves, the lower age limit was set at 20 years of age.
2) The study will be conducted in accordance with Good Clinical Practice (GCP).
3), 4) The study will investigate DPNP.
5), 6) In order to assess the efficacy of the investigational product appropriately, the study will be limited to subjects who experience pain of moderate or greater intensity.

4.1.3 Exclusion Criteria

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

1) At screening, a pain scale of ≥ 90 mm on VAS of SF-MPQ
2) At randomization, a pain scale of ≥ 90 mm on VAS of SF-MPQ, or at least a daily pain score of ≥ 9 during observation period
3) HbA1c (National Glycohemoglobin Standardization Program) > 10.0% at screening
4) Uncontrolled blood glucose at screening or randomization that may require changes in diabetes treatment (non-insulin drug therapy, exercise therapy, diet therapy) during the study
5) Other severe pain at screening or randomization, unrelated to DPN, that may confound the assessment of DPNP
6) Neurologic disorders at screening or randomization, unrelated to DPN, that may confound the assessment of DPNP
7) Major psychiatric disorders at screening or randomization
8) Amputation of lower limb parts, other than toes, prior to screening or randomization

9) Use of prohibited concomitant drugs within 7 days or change of restricted concomitant drugs within 30 days prior to screening
10) Skin conditions that could confound the assessment of DPNP
11) Previous administration of pregabalin ≥ 300 mg/day or gabapentin ≥ 1200 mg/day, declared lack of effect
12) Creatinine clearance (using the Cockcroft-Gault equation) < 60 mL/min at screening
13) Malignancy other than basal cell carcinoma within the past 2 years prior to screening
14) Clinically significant unstable neurologic, ophthalmologic, hepatobiliary, respiratory, hematologic illness or unstable cardiovascular disease (eg, severe hypotension, uncontrolled cardiac arrhythmia, or myocardial infarction) within 12 months prior to screening
15) Clinically significant findings on electrocardiogram (ECG) at screening
16) History of pernicious anemia, untreated hypothyroidism, or human immunodeficiency virus infection
17) Known history of positive Hepatitis B antigen or Hepatitis C antibody
18) Pregnancy, potential pregnancy, breast feeding, or subject unwilling to take reliable contraceptive measures during the study or for 4 weeks after study completion
19) Known hypersensitivity to pregabalin or gabapentin
20) Participation in another clinical study, either currently or within 30 days prior to providing of informed consent
21) Experience of participating DS-5565 clinical study and receiving investigational product
22) Abuse of illicit drugs or alcohol within one year prior to screening
23) Response of "yes" to any of the questions on the Columbia-Suicide Severity Rating Scale (C-SSRS) at screening or randomization in relation to events occurring within the past 12 months
24) Previous treatment with drugs that could cause irreversible retinal degeneration
25) At screening, clinical laboratory values exceeding limits listed in Table 4-1

Table 4-1 Hematology/Blood Chemistry Limits

Hematology	Hemoglobin	<10 g/dL Females <12 g/dL Males
	Hematocrit	<32% Females <35% Males
	Platelet Count	<100 000/mm^3
	WBC	<2500/mm^3
	Absolute Neutrophil Count	<1500/mm^3
Blood Chemistry	AST (GOT)	>2.0 × ULN
	ALT (GPT)	>2.0 × ULN
	ALP	>1.5 × ULN
	T-Bil	>1.2[a] × ULN
	BUN	>1.5 × ULN
	Creatine Kinase	>3.0 × ULN
	Serum Creatinine	>1.6 mg/dL (>141.4 mol/L)

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

26) The subject who is considered inappropriate for the study at the discretion of the investigator or sub-investigator
27) Response of "yes" to the suicidality question (current or past) on the Major Depressive Episode Module (Module A) or response of "yes" to any question of B1b, B3 through B11c, B13, or B14 in the Suicidality Module (Module B) on the Mini-international Neuropsychiatric Interview (MINI) Interview (Version 6.0) at screening

Rationale

1), 2) These criteria were selected so that efficacy could not be appropriately assessed in these subjects, because reporting extreme pain may reflect psychosocial distress, and may reflect patients' lack of comprehension to accurately rate their pain.
3), 4), 5), 6), 7), 8), 9), 10) These criteria were selected so that efficacy and safety could be appropriately assessed in subjects.
11), 21) These criteria were selected out of consideration for efficacy assessment in subjects.
12), 13), 14), 15), 16), 17), 18), 19), 20), 22), 23), 24), 25), 26), 27) These criteria were selected out of consideration for the safety of subjects.

4.2 Subject Withdrawal

Data from all randomized subjects are important to achieve study objectives, and subjects should be encouraged to adhere to protocol instructions and visit schedules. However, in accordance with the Declaration of Helsinki and other applicable regulations, a subject has the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the study physician or at the study site. The investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants such action. The sponsor or regulatory authorities also may request termination of the study at any time due to safety issues or concerns related to study conduct.

4.2.1 Withdrawal Criteria

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

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

4.2.2 Reasons for Withdrawal

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

For subjects withdrawn prior to randomization but after signing informed consent

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

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

- AE
- Death
- LOE
- Lost to follow-up
- Protocol violation
- Pregnancy
- Study terminated by sponsor
- Withdrawal by subject (eg, AE, LOE, Other)
- Other

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

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

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

All subjects who are withdrawn from the study should complete protocol-specified withdrawal procedures (see Section 4.2.3 and Section 6.4).

4.2.3 Withdrawal Procedures

If a subject withdraws or is withdrawn from the study before the completion of investigational product administration, appropriate measures will be implemented. In addition, to the extent that the subject's cooperation can be obtained, all observations and

tests scheduled for the End of Treatment/Early Termination Visit (Visit 10) will be conducted, assessments will be made at that time point, all observations and tests scheduled for the Post-treatment Follow-up Visit (Visit 11) will be conducted, and assessments will be made 5 to 14 days after the last dose. This will be done for all subjects who were treated with even one dose of the investigational product. If the withdrawal was due to AEs, the outcome for that subject will be recorded to the extent possible in the Case Report Form (CRF) (see Section 9.1.4). If the withdrawal was due to suicidal behavior and/or suicidal ideation, appropriate measures will be implemented such as referring the subject to a specialist.

4.2.4 Stopping Rules for the Study

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

Hepatic events study stopping rules:

If there is one adjudicated Hy's law case on DS-5565 in any of the Phase 3 studies and/or the entire Phase 3 program.

Suicide study stopping rules:

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

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

5. TREATMENT ADMINISTERED

5.1 Investigational Products

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

5.1.1 Study Treatments

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

5.1.1.1 Investigational Product

Investigational product code: DS-5565

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

Content and dosage form:

Name of investigational product	Content and dosage form
DS-5565 Tablets 5 mg	White film-coated tablet containing 5 mg of the free form of DS-5565
DS-5565 Tablets 10 mg	White film-coated tablet containing 10 mg of the free form of DS-5565
DS-5565 Tablets 15 mg	White film-coated tablet containing 15 mg of the free form of DS-5565

5.1.1.2 Investigational Product Placebo

Content and dosage form:

Name of investigational product	Content and dosage form
DS-5565 Tablets Placebo 3	White film-coated matching placebo tablet for DS-5565 Tablets 5 mg
DS-5565 Tablets Placebo 4	White film-coated matching placebo tablet for DS-5565 Tablets 10 mg and DS-5565 Tablets 15 mg

5.1.2 Dosing Regimens for the Study

The duration of investigational product administration will be 14 weeks, consisting of a titration period and a fixed-dose period. As Table 5-1 shows, the treatment period will begin at bedtime on Day 1 (Visit 2) and will continue until the morning of Day 99 (Visit 10). During the treatment period, 1 tablet either DS-5565 or matching placebo will be administered orally twice daily (in the morning and at bedtime). The subject must select the administration timing, either fasted or fed in the morning at randomization

(Visit 2), and it will be followed during the treatment period.

Table 5-1 Method of Administration During the Treatment Period

Group	Day 1		Day 2 to 7		Day 8		Day 9 to 14		Day 15		Day 16 to 98		Day 99	
	Morning	Bedtime	Morning	Bedtime	Morning	Bedtime	Morning	Bedtime	Morning	Bedtime	Morning	Bedtime	Morning	Bedtime
DS-5565 15 mg QD	—	5	0	5	0	10	0	10	0	15	0	15	0	—
DS-5565 10 mg BID	—	5	5	5	5	10	10	10	10	10	10	10	10	—
DS-5565 15 mg BID	—	5	5	5	5	10	10	10	10	15	15	15	15	—
Placebo	—	0	0	0	0	0	0	0	0	0	0	0	0	—

5.1.3 Method of Assigning Subjects to Treatments and Blinding

5.1.3.1 Method of Assigning the Investigational Product to Subjects

The subjects who are considered to be eligible for participation in the study, on the basis of evaluations prior to randomization, will be randomly assigned to placebo, or one of the DS-5565 arms (15 mg QD, 10 mg BID, or 15 mg BID) with randomization ratio of 2:1:1:1 in accordance with the IWRS. The randomization will be stratified with the factors of baseline ADPS (< 6.0 or ≥ 6.0). The randomization schedule for the IWRS will be generated by the independent biostatistician.

After obtaining written informed consent, the investigator or sub-investigator will access the IWRS to register the subject and input the subject's information. At the randomization visit, the investigator or sub-investigator will enter the eligibility criteria data to obtain a unique study drug identifier that will be assigned to the subject.

The investigator or sub-investigator will dispense the investigational product to each subject in accordance with the individual study drug identifier from the IWRS. The investigational product for each study drug identifier will be dispensed specifically to 1 subject, and will not be used by any other subjects.

5.1.3.2 Blinding

The study is a double-blind study using DS-5565 and placebo, which will be prepared to be indistinguishable in appearance from the investigational product. The study will be blinded for those who will be involved in the study (subjects, investigators, sub-investigators, other staff members related to the clinical study, the sponsor, etc.), with the exception of the independent biostatistician, the independent sub-functional lead of

biostatistics (ISFLB), and staff members related to packaging operation and quality assurance.

Randomization schedule will be generated by the independent biostatistician and approved by the ISFLB. The independent biostatistician will share the randomization schedule with personnel specified in the randomization schedule request form for the investigational product assignment and keeping it strictly confidential until the study is unblinded.

Until the study is unblinded, the person responsible for investigational product monitoring at the drug concentration monitoring facility will use a different identification number from the subject identification code and the study drug identifier to maintain blinded manner when reporting the outcome of measurements to the sponsor.

5.1.3.3 Preparation and Management of Emergency Codes

Independent biostatistician or ISFLB will prepare emergency codes that can be unblinded by the study drug identifier, so that administered treatment of the patient can be identified in case of emergency.

The emergency codes will be retained in dedicated IWRS managed by Bell Medical Solutions, Inc.

The emergency codes must not be unblinded for the cases other than the states of Section 5.1.3.4.

5.1.3.4 Procedures for Emergency Unblinding

1) If emergency unblinding is deemed necessary by the investigator or sub-investigator:
   - When it is deemed necessary to unblind the treatment assignments to treat AEs, the investigator or sub-investigator will request the sponsor to determine the appropriateness of the emergency unblinding after explaining the reason through the IWRS.
   - The sponsor will determine the appropriateness of the emergency unblinding in consultation with medical expert as required.

     i. When emergency unblinding is deemed appropriate by the sponsor

     - When unblinding is deemed appropriate, the sponsor will notify the

investigator or sub-investigator of the fact and the reason through the IWRS.

- The sponsor will request the investigator or sub-investigator to prepare the CRF of the appropriate patient.
- The sponsor issues the password for confirming the emergency code of the appropriate patient on the IWRS through the IWRS.
- The investigator or sub-investigator receive the password, enter their passwords to login, and then confirm the emergency code of the appropriate patient.
- Information about the treatment assignment **must be** restricted to only designated study site staff/personnel who are providing immediate care to the subject.
- Any documentation of the treatment assignment must be maintained separately (ie, a secured file). The information must not be included in the subject's source files to ensure the treatement assignment will remain blinded to the study monitor and other study personnel not involved with the subject's immediate care.

ii. When emergency unblinding is not deemed appropriate by the sponsor

- When unblinding is determined not appropriate, the sponsor will notify the investigator or sub-investigator of the fact and the reason through the IWRS.

2) When emergency unblinding is deemed necessary by the sponsor

- When emergency unblinding is deemed necessary in consultation with medical expert in case of such as occurrence of a potential safety problem for the patients, the sponsor will notify the investigator or sub-investigator of the unblinding.
- The sponsor will request the investigator or sub-investigator to prepare a CRF of the appropriate patient.
- The sponsor relies the issuance of the password for confirming the emergency code of the appropriate patient on the IWRS to the investigator or sub-investigator through the IWRS.
- The sponsor receives the password, enters the password to login, and then confirm the emergency code of the appropriate patient.

5.1.3.5 Subject Replacement

No subjects will be replaced in this study.

5.1.4 Method of Assessing Treatment Compliance

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

5.1.5 Labeling and Packaging

DS-5565 and/or matching placebo, will be packaged in aluminum blister packs. Packages for the treatment period will be prepared for the combinations shown in Table 5-2, Table 5-3, and Table 5-4. One box will be prepared for each subject. Each box will contain the investigational product for that subject during the treatment period. The packaging will be clearly labeled "For Clinical Study Use Only," and will show the display name of the investigational product, the investigational-product-manufacturing code, the study drug identifier, the name and address of the sponsor, and the expired date of the investigational product in accordance with local regulations. Each wallet card of the investigational product will contain sufficient extra doses to cover the permitted visit window for each subject.

Table 5-2 Drug Combinations During the Treatment Period (Week 1)

Treatment group	Investigational product combination	
	Morning	Bedtime
DS-5565 15 mg QD	(P)	(5)
DS-5565 10 mg BID	(5)	(5)
DS-5565 15 mg BID	(5)	(5)
Placebo	(P)	(P)

(P) DS-5565 matching placebo tablet

(5) DS-5565 5 mg tablet

Table 5-3 Drug Combinations During the Treatment Period (Week 2)

Treatment group	Investigational product combination	
	Morning	Bedtime
DS-5565 15 mg QD	(P)	(10)
DS-5565 10 mg BID	(10)	(10)
DS-5565 15 mg BID	(10)	(10)
Placebo	(P)	(P)

(P) DS-5565 matching placebo tablet

(10) DS-5565 10 mg tablet

Table 5-4 Drug Combinations During the Treatment Period (Week 3 to Week 14)

Treatment group	Investigational product combination	
	Morning	Bedtime
DS-5565 15 mg QD	(P)	(15)
DS-5565 10 mg BID	(10)	(10)
DS-5565 15 mg BID	(15)	(15)
Placebo	(P)	(P)

(P) DS-5565 matching placebo tablet

(10) DS-5565 10 mg tablet

(15) DS-5565 15 mg tablet

5.1.6 Storage

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

5.1.7 Drug Accountability

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

5.2 Concomitant Medications and Treatments

Any concomitant medications except rescue medication (see Section 5.2.3) and any concomitant treatments conducted to a subject during the period from the time of obtaining informed consent until Visit 11, whether permitted or not, will be documented in the CRF. The route of administration, the total daily dose, the duration of use, the indication for use, and the classification of therapies will also be documented in the CRF.

5.2.1 Prohibited Concomitant Medications

The following drugs are prohibited for concomitant use from the screening (Visit 1) through the post-treatment follow-up (Visit 11). The patients given drugs that could

cause irreversible retinal degeneration must be excluded. After informed consent is obtained, subjects who are under treatment with the following prohibited concomitant drugs will undergo a washout period of 7 days or more. Visit 1 will occur after completion of this washout period.

1) Pregabalin
2) Antiepileptics (gabapentin, carbamazepine, etc.)
3) Antidepressants (other than selective serotonin reuptake inhibitors)
4) Hypnotics, anxiolytics (other than ultrashort acting drug [triazolam, zopiclone, zolpidem tartrate])
5) Opioids
6) Tramadol
7) Neurotropin®
8) N-methyl-D-aspartate receptor (NMDA) antagonists (dextromethorphan, ketamine, memantine, etc.)
9) Non-steroidal anti-inflammatory drugs (except topical product for other than disease site of DPN)
10) Muscle relaxants
11) Topical capsaicin (except topical product for other than disease site of DPN)
12) Local anesthetics (lidocaine, etc.) (except topical product for other than disease site of DPN)
13) Na channel blockers (mexiletine, etc.)
14) Centrally acting sympatholytic agents (clonidine, etc.)
15) Steroids (except topical product for other than disease site of DPN)
16) cilostazol, prostaglandin (except topical product for other than disease site of DPN)
17) Chinese herbal medicines with analgesic effects on neuropathic pain (Life-preserving kidney-qi pill, Peony and licorice decoction, Eight-ingredient pill with rehmannia, etc.)
18) Vitamins B1 and B12 (except topical product for other than disease site of DPN)
19) α-lipoic acid
20) γ-linolenic acid (evening primrose oil)
21) Aldose reductase inhibitors
22) Drugs that could cause irreversible retinal degeneration (phenothiazine antipsychotics, deferoxamine, quinine, quinidine, ethambutol, voriconazole, etc.)
23) Other investigational products

5.2.2 Restricted Concomitant Medications

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

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

5.2.3 Rescue Medications

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

5.2.4 Prohibited Concomitant Therapies

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

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

5.2.5 Other

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

6. STUDY PROCEDURES

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

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

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

6.1 Screening (Visit 1, 7 days prior to randomization)

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

- Evaluate inclusion criteria and exclusion criteria
- Record demographics (birth date, sex, type of diabetes, duration of diabetes, duration of DPN, duration of DPNP), medical/surgical history related to exclusion criteria and alcohol history
- Provide explanation regarding electronic patient diary, and providing of electronic diary
- Complete SF-MPQ
- Complete HADS
- Measure body height and weight
- Perform physical examination
- Perform evaluation of edema
- Perform full neurological examination
- Perform ophthalmologic examination
- Measure blood pressure and pulse rate
- Perform 12-lead ECG
- Collect blood and urine samples for laboratory tests
- Collect blood sample for evaluation of fasting blood glucose levels
- Collect blood sample for evaluation of HbA1c

- Evaluate AEs
- Complete C-SSRS
- Perform pregnancy test (only in women of childbearing potential)
- Evaluate prior drug treatment, concomitant drugs, and concomitant therapy
- Complete Module A and B on MINI Interview (Version 6.0)

6.2 Randomization (Visit 2, Day 1)

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

- Evaluate inclusion criteria and exclusion criteria
- Review electronic patient diary data
- Complete SF-MPQ
- Complete the modified BPI-SF
- Complete MOS sleep scale
- Complete HADS
- Complete 36-item short form health survey (SF-36)
- Measure body weight
- Perform physical examination
- Perform abbreviated neurological examination
- Measure blood pressure and pulse rate
- Collect blood and urine samples for laboratory tests
- Evaluate AEs
- Complete C-SSRS
- Record and evaluate concomitant drugs and concomitant therapy
- Confirm eligibility and randomization
- Issue the investigational product
- Select and record the drug administration in the morning (fasted/fed) during the study treatment

6.3 Treatment Period

The treatment period will be 14 weeks in duration.

6.3.1 Visit 3 and Visit 4

From Visit 2 to Visit 4, subjects will come to the study site every week (Visit 3, Visit4). The investigator or sub-investigator will confirm tolerability and review continuation of

the treatment before issuing the new investigational product. The following activities and/or examinations will be performed at Visit 3 and Visit 4.

- Review electronic patient diary data
- Complete SF-MPQ
- Complete HADS
- Measure body weight
- Perform physical examination
- Perform abbreviated neurological examination
- Measure blood pressure and pulse rate
- Collect blood and urine samples for laboratory tests
- Evaluate AEs
- Complete C-SSRS
- Record and evaluate concomitant drugs and concomitant therapy
- Collect unused investigational product, and record and review drug-taking compliance
- Record the date of the first dose taken
- Issue the investigational product
- Collect blood sample for PK analysis

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

From Visit 4 to Visit 9, subjects will come to the study site once every 2 weeks (Visit 5, Visit 6, Visit 7, Visit 8, and Visit 9). The investigator or sub-investigator will confirm tolerability and review continuation of the treatment before issuing the new investigational product. The following activities and/or examinations will be performed at Visit 5, Visit 6, Visit 7, Visit 8, and Visit 9.

- Review electronic patient diary data
- Complete SF-MPQ
- Complete HADS
- Measure body weight
- Perform physical examination
- Perform abbreviated neurological examination
- Measure blood pressure and pulse rate
- Collect blood and urine samples for laboratory tests
- Collect blood sample for evaluation of HbA1c (Visit 6 only)
- Collect blood sample for evaluation of fasting blood glucose levels (Visit 6 only)

- Evaluate AEs
- Complete C-SSRS
- Record and evaluate concomitant drugs and concomitant therapy
- Collect unused investigational product, and record and review drug-taking compliance
- Issue the investigational product
- Collect blood sample for PK analysis (Visit 6 and Visit 8 only)

6.4 End of Treatment/Early Termination (Visit 10)

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

- Collect and review electronic patient diary data, and collecting electronic diary
- Complete SF-MPQ
- Complete the modified BPI-SF
- Complete PGIC
- Complete MOS sleep scale
- Complete HADS
- Complete SF-36
- Complete Evaluation of Symptoms
- Measure body weight
- Perform physical examination
- Perform evaluation of edema
- Perform full neurological examination
- Perform ophthalmologic examination
- Measure blood pressure and pulse rate
- Perform 12-lead ECG
- Collect blood and urine samples for laboratory tests
- Collect blood sample for evaluation of HbA1c
- Collect blood sample for evaluation of fasting blood glucose levels
- Complete C-SSRS
- Perform pregnancy test (only in women of childbearing potential)
- Evaluate AEs
- Record and evaluate concomitant drugs and concomitant therapy
- Collect unused investigational product, and record and review drug-taking compliance

- Record the date of the last dose taken
- Collect blood sample for PK analysis

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

Follow-up observations will be conducted 7 days after the completion of administration (Visit 11). The following activities and/or examinations will be performed at post-treatment follow-up. No follow-up observation is required for subjects enrolled in an open-label extension study.

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

7. EFFICACY ASSESSMENTS

7.1 Primary Efficacy Variable(s)

Pain score[7]

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

7.2 Secondary Efficacy Variable(s)

1) Response rate

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

2) Short-Form McGill Pain Questionnaire[8]

At Visit 1, Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, Visit 8, Visit 9, and Visit 10, subjects will provide a self-assessment using the SF-MPQ. The SF-MPQ consists of 3 parts:

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

3) Modified Brief Pain Inventory (Short Form)[9]

At Visit 2 and Visit 10, subjects will provide a self-assessment using the modified BPI-SF. The modified BPI-SF will be used to assess the severity of pain and the impact of pain on daily function. Subjects will select the number that most closely represents their pain experience on an 11-point scale in two categories: severity, scored from 0 (no pain) to 10 (pain as bad as you can imagine), and impact on daily functions, scored from 0 (does not interfere) to 10 (completely interferes).

Severity of pain

- Worst pain in the last 24 hours

- Least pain in the last 24 hours
- Average pain
- Pain right now

Impact on daily functions

- General activity
- Mood
- Walking ability
- Normal work (includes both work outside the home and housework)
- Relations with other people
- Sleep
- Enjoyment of life

4) Patient Global Impression of Change[7]

At Visit 10, subjects will provide a self-assessment in comparison to Visit 2, using the 7-point scale in the PGIC.

1: very much improved
2: much improved
3: minimally improved
4: no change
5: minimally worse
6: much worse
7: very much worse

5) Sleep-interference Score

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

6) Medical Outcomes Study sleep scale[10,11]

At Visit 2 and Visit 10, subjects will provide a self-assessment using the MOS sleep scale. The MOS sleep scale is based on questions about sleep quality during the past 4 weeks, and consists of 3 parts:

- The average time required to fall asleep
  - 0-15 minutes.....1
  - 16-30 minutes.....2
  - 31-45 minutes.....3
  - 46-60 minutes.....4
  - More than 60 minutes.....5
- The average hours of sleep per night, given as number of hours per night.
- 10 questions that are given a score of 1 (all of the time) to 5 (none of the time), based on sleep disturbance in the following areas: difficulty in falling asleep or remaining asleep, difficulty in staying awake during the day, difficulty in breathing, and snoring during sleep.

7) Hospital Anxiety and Depression Scale[12]

At Visit 2 and Visit 10, subjects will provide a self-assessment using the HADS, which will be adopted as efficacy evaluation. The HADS consists of 7 items to score depression (4-point scale) and 7 items to score anxiety (4-point scale). The subject will respond to each item on the questionnaire.

8) SF-36[13]

At Visit 2 and Visit 10, subjects will provide a self-assessment using the SF-36. The SF-36 questionnaire yields an 8-scale profile of the subject's self-assessed QOL in the following categories: Physical Functioning (3-point scale, 10 items), Role-Physical (5-point scale, 4 items to score role limitations caused by physical problems), Bodily Pain (6-point scale, 1 item; 5-point scale, 1 item), General Perception of Health (5-point scale, 5 items), Vitality (5-point scale, 4 items), Social Functioning (5-point scale, 2 items), Role-Emotional (5-point scale, 3 items to score role limitations caused by emotional problems) and Mental Health (5-point scale, 5 items). The subject will respond to each item on the questionnaire.

9) Evaluation of Symptoms[6]

At Visit 10, subjects will provide a self-assessment of "pain excepting 'tingling' and 'pins

and needles' ", " 'tingling' or 'pins and needles' ", and "dysesthesia" in their feet in comparison to baseline, using the following 4-point scale.

1: improved
2: no change
3: worse
4: no symptoms

8. PHARMACOKINETIC AND BIOMARKER ASSESSMENTS

8.1 Pharmacokinetic Variable(s)

Blood samples will be taken at the sites capable of blood sampling. Blood sample will be collected one time each at Treatment Period Visits (Visit 3, Visit 4, Visit 6, and Visit 8) and at End of Treatment/Early Termination Visit (Visit 10). At least one blood sample must be collected within 4 hour after administration. Blood samples will be collected in accordance with the procedures described in Section 17.2. In the CRF, the following will be recorded:

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

Although PK samples will be taken for all subjects, drug concentration will be measured only on subjects receiving DS-5565.

8.2 Biomarker Variable(s)

No biomarker analysis will be performed.

9. SAFETY ASSESSMENTS

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

9.1 Adverse Events

9.1.1 Definition of Adverse Event

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

Any symptom that the investigator or sub-investigator considers associated with DPN will be evaluated as an efficacy variable and will not be regarded as an AE. However, if the symptom is considered potentially related to the investigational product, such symptom will be regarded as an AE. If any pre-existing symptom or disease is aggravated during the study period, the aggravation will be reported as an AE, and the date of confirming the aggravation will be considered the date of event onset.

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

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

- Increase in ALT or AST $\geq$ 5 x 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 T-Bil $\geq$ 2 x ULN
- ALT or AST $\geq$ 3 x ULN associated with a clinical presentation suggestive of liver injury (ie, including the appearance of fatigue, nausea, vomiting, jaundice, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia)
- Serious hepatobiliary adverse event
- Severe hepatobiliary adverse event

- Hepatobiliary Adverse event leading to Discontinuation
- Any transaminase elevation associated with a clinical presentation suggestive of Liver injury
- An elevation of ALT or AST >= 3 x ULN (without clinical presentation suggestive of liver injury)
- AE related to suicide (if there are any "yes" responses to any of the questions in the C-SSRS)

9.1.2 Items to Be Investigated Concerning Adverse Events

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

Table 9-1 Items to be Investigated for Adverse Event

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

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

Items reviewed	Content of review	
Relationship to the investigational product	Classification of relationship (in accordance with the following classifications of relationship), reason for that assessment	
Classification of relationship	Related	• The AE follows a reasonable temporal sequence from investigational product administration, and cannot be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, concomitant medications). • The AE follows a reasonable temporal sequence from investigational product administration, and is a known reaction to the drug under study or its chemical group, or is predicted by known pharmacology.
	Not related	• The AE does not follow a reasonable temporal sequence from investigational product administration, or can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, concomitant medications).
Other action taken for event	None	No treatment was required.
	Medication required	Prescription and/or over-the-counter medication was required to treat the AE.
	Hospitalization or prolongation of hospitalization required	Hospitalization was required or prolonged due to the AE, whether or not medication was required.
	Other	

9.1.3 Definition of Adverse Drug Reaction

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

9.1.4 Actions to Be Taken When Adverse Events Occur

When an AE occurs, the investigator or sub-investigator will provide appropriate treatment, will report the AE to the sponsor if necessary, and to the extent possible will monitor progress until the subject recovers or the AE is resolved or relieved. If it appears unlikely from a medical perspective that the subject will recover, this will be explained to the subject, and monitoring of the subject as a part of the clinical trial will be concluded (although the treatment for the AE will be continued). In addition, clinical trial follow-up will be terminated and the clinical trial will be concluded if the investigator or sub-investigator decides further follow-up is unnecessary for the AE

because there is no relationship between the AE and the investigational product, or if the subject refuses further follow-up.

9.2 Actions to Be Taken When Serious Adverse Events Occur

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

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

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

The following types of events should be reported to the sponsor as promptly as possible after becoming aware of the event via the eCRF.

- Severe hepatobiliary adverse event
- Hepatobiliary Adverse event leading to Discontinuation
- Any transaminase elevation associated with a clinical presentation suggestive of Liver injury
- An elevation of ALT or AST >= 3 x ULN (without clinical presentation suggestive of liver injury)

9.3 Exposure In Utero During Clinical Studies

Daiichi Sankyo must be notified of any subject who becomes pregnant while receiving or at the time of discontinuing the investigational product. All pregnancies must be

followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the investigator to report any pregnancy in a subject using the Exposure In Utero (EIU) Reporting form. The investigator will contact the study monitor to obtain the EIU Reporting Form upon learning of a pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (ie, post-partum complications, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, including congenital anomaly in an aborted fetus), the investigator should follow the procedures for reporting SAEs.

9.4 Clinical Laboratory Evaluations

The study site staff will collect blood and urine specimens for routine laboratory tests at specified times. Specimens will be stored under conditions stipulated in the Sample Handling Manual until they are transported for measurement. Specimens will be transported and measured by a central laboratory. Table 9-2 summarizes the laboratory parameters to be assessed and the times of assessment.

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

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

Table 9-2 Laboratory Parameters to be Assessed, and Time of Assessment

	Parameters	Time of assessment
Hematology	WBC, RBC, hemoglobin, hematocrit, platelet count, differential leukocyte (neutrophil, eosinophil, basophil, monocyte, lymphocyte) counts, reticulocyte count	Visit 1, Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, and Visit 11
Blood chemistry	Total protein, albumin, A/G ratio, T-Bil, AST (GOT), ALT (GPT), ALP, γ-GT (γ-GTP), LDH, BUN, creatinine, uric acid, creatine kinase, total cholesterol, triglycerides, Na, K, Cl, Ca, Mg, inorganic phosphorus, bicarbonate, CRP	
Urinalysis	Standard urinalysis, including microscopic examination Specific gravity, pH, protein, glucose, ketones, urobilinogen, occult blood, RBC, WBC, bilirubin	
HbA1c	HbA1c	Visit 1, Visit 6, and Visit 10
Fasting blood glucose	Fasting blood glucose level	Visit 1, Visit 6, and Visit 10
Pregnancy	Qualitative test (urine)	Visit 1 and Visit 10

As described in Section 4.2.1, increases in aminotrasferases have been observed in the DS-5565 development program to date. Special monitoring of such elevations during Phase 3 is described below. The Hepatic Adjudication Committee (HAC) charter includes a process by which selected cases will be adjudicated by a liver disease specialist (Section 11.10). In cases of liver laboratory abnormalities, it is important to ensure that the nature and the extent of liver injury is identified and study subjects are monitored until the liver laboratory assessments return to normal. Subjects who have any transaminase elevation associated with a clinical presentation suggestive of liver injury (ie, including the appearance of fatigue, nausea, vomiting, jaundice, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia) or an elevation of ALT or AST $\geq$ 3 x ULN (without clinical presentation suggestive of liver injury) at any visit should be monitored closely, according to the following:

- Repeat liver tests of at least all four of the usual serum measures (ALT, AST, alkaline phosphatase (ALP), and total bilirubin at least 2 times weekly (the first repeat should be within 48 to 72 hours of initial abnormality) until values have decreased to < 2 x ULN, then at least every 1 or 2 weeks until resolution or return to baseline. An additional 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.

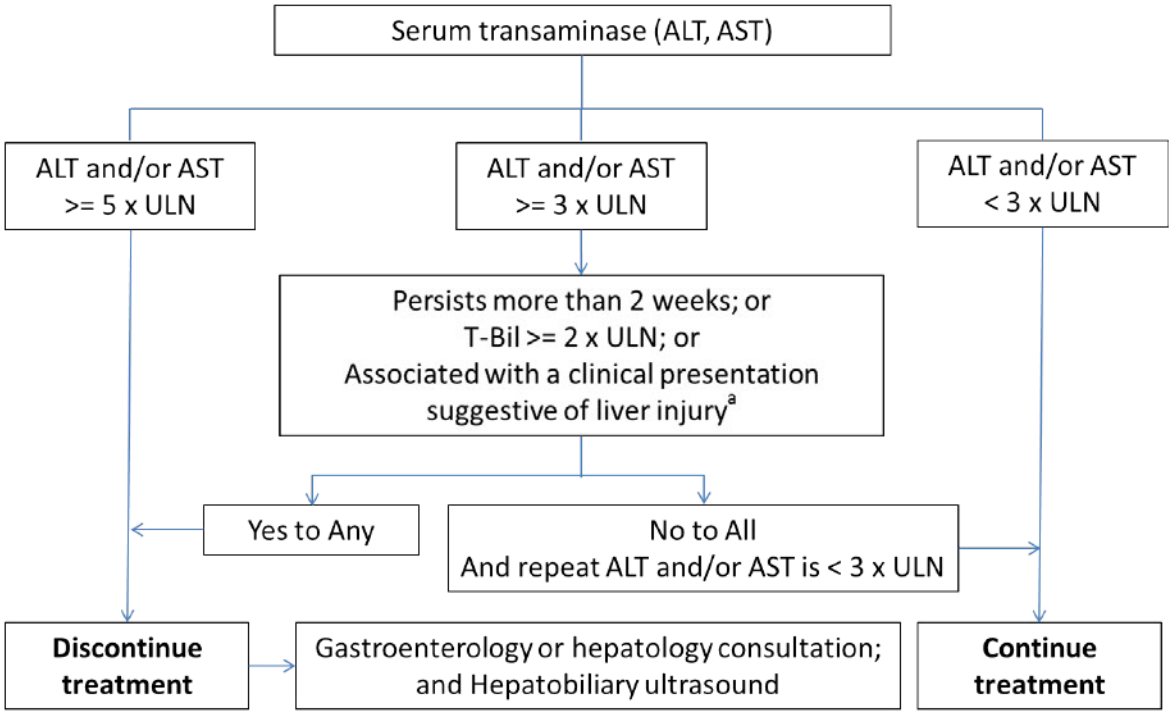
- Review or obtain a detailed history of symptoms and prior or concurrent diseases.
- Review or obtain a history of the use of concomitant drugs, including nonprescription medications, herbal and dietary supplements, alcohol, recreational drugs, and special diets.
- Rule out alcoholic hepatitis; non-alcoholic steatohepatitis (NASH); hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtain a history of exposure to environmental chemical agents.
- Perform additional liver function tests (LFTs) (eg, serum lactate dehydrogenase (LDH), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (γ-GT [γ-GTP]), prothrombin time [PT]), evaluations for potential viral etiologies (including hepatitis A, B, C, E; cytomegalovirus [CMV]; Epstein-Barr virus [EBV]) and autoimmune etiologies (anti-nuclear antibody [ANA], anti-smooth muscle antibody [ASMA], anti-mitochondrial antibody [AMA]).

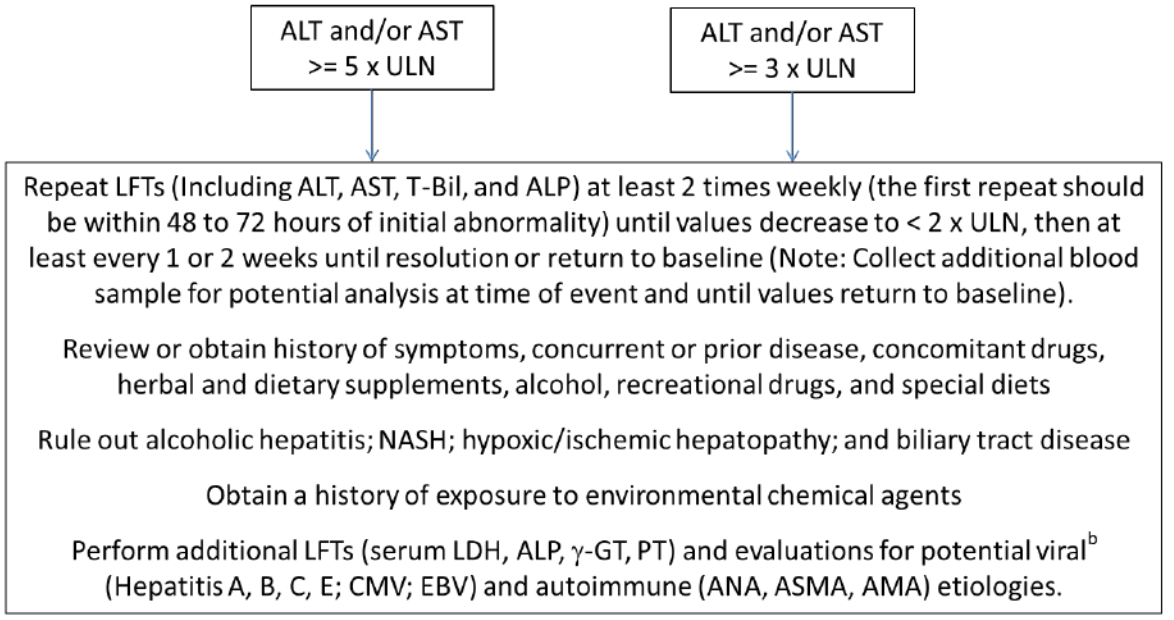
Combined elevations of aminotransferases and bilirubin meeting the criteria of a potential Hy's Law case [ALT or AST ≥ 3 x ULN with simultaneous total bilirubin ≥ 2 x ULN], either serious or non-serious and whether or not causally related, should always be reported to the sponsor within 24 hours (refer to Section 9.2), 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/Guidance/UCM174090.pdf). These events should be reported as soon as possible following the procedures outlined in Section 9.2 for SAE reporting. The sponsor will be responsible for reporting the case(s) to the FDA.

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

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

- Gastroenterology or hepatology consultation
- Hepatobiliary ultrasound





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

9.5 Vital Signs

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

9.6 Electrocardiograms

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

9.7 Physical Findings

9.7.1 Body Height and Weight

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

9.7.2 Physical Examinations

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

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

9.7.3 Evaluation of Edema

At Visit 1 and Visit 10, evaluation of edema will be performed including physical

examination and/or pitting. Results (presence or absence of edema and expression site) will be recorded in the CRF.

9.8 Other Safety Assessments

9.8.1 Neurological Examination

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

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

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

9.8.2 Ophthalmologic Examination

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

9.8.3 Columbia-Suicide Severity Rating Scale[14]

The C-SSRS is a tool designed to systematically assess and track suicidal AEs (behavior and ideation). The C-SSRS assesses lifetime suicidality during an initial baseline evaluation using standardized questions, and then prospectively monitors ideations and

behaviors at subsequent follow-up assessments throughout the trial. The reviewer is an investigator or sub-investigator who has completed training prior to the study using the training DVD. The C-SSRS will be administered by the investigator or sub-investigator at each visit. Answers to all relevant questions will be recorded in the CRF. If the subject is judged to have suicidal behavior and/or suicidal ideation, appropriate measures will be implemented such as referring the subject to a specialist as described in the withdrawal procedures (see Section 4.2.3).

9.8.4 Hospital Anxiety and Depression Scale[12]

At each visit, subjects will provide a self-assessment using the HADS. The HADS consists of 7 items to score depression (4-point scale) and 7 items to score anxiety (4-point scale). The subject will respond to each item on the questionnaire. Based on the results, the investigator will check for the presence or absence of depression and/or anxiety. If the subject is judged to have an AE, appropriate measures will be implemented such as referring the subject to a specialist. Results will be recorded in the CRF.

9.8.5 Pregnancy test

Pregnancy tests (urine tests) will be conducted at the stipulated times (Visit 1 and Visit 10), for women of child-bearing potential only. All female subjects will be considered as women of child-bearing potential unless they have undergone surgical sterilization (with documented bilateral oophorectomy) or are postmenopausal and have experienced no menses within the previous 6 months. The subject is considered to be postmenopausal when 12 consecutive months of absence of menstruation is confirmed with no pathological or physiological factors. Results will be recorded in the CRF.

10. OTHER ASSESSMENTS

No other assessments will be performed.

11. STATISTICAL METHODS

11.1 Objective

The primary objective is to compare the change from baseline to Week 14 (Visit 10) in ADPS for 10 mg BID and 15 mg BID of DS-5565 against placebo. The secondary objectives are shown in section 2.1.2.

.

11.2 General Statistical Considerations

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

The modified intent-to-treat (mITT) analysis set will be used as a primary efficacy analysis set for all efficacy analyses and the per-protocol set (PPS) will be used for sensitivity analysis. All safety analyses and pharmacokinetic analyses will be conducted for the safety analysis set and PK analysis set, respectively.

The primary imputation will be based on “nonfuture dependence" model using the pattern mixture approach under the missing not at random (MNAR) mechanism for the missing weekly ADPS data[19 - 21]. Reason for dropout together with the time of dropout will be used for constructing the missing data pattern. Detail will be at Section 11.5.1 and in the SAP.

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

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

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

All hypothesis testing will provide the *P* values and their corresponding two-sided 95% confidence intervals if applicable. The significance level is 0.05 (two-sided) for all hypothesis testing. The type I error rate will be controlled at less than 0.05 for the multiple comparisons of the primary endpoint of ADPS at Week 14 between each DS-5565 arm (15 mg QD, 10 mg BID, or 15 mg BID) and placebo, using combination approach of Bonferroni-Holm method and gate-keeping procedure (see Section 11.5.1). No adjustment for multiple comparisons will be made for the secondary efficacy analyses.

Analysis for the change from baseline, including the shift table, will be conducted for the

subjects who have an available baseline value and at least one post-randomization value.
Subgroup analyses by country (eg, Japan, Korea, and Taiwan) will be conducted for some of efficacy and safety analyses specified in the SAP.
PK analysis will be detailed in the PK analysis plan (PAP).
A detailed SAP and PAP describing the methodology to be used in the final analysis will be prepared before data unblinding. A change in the planned statistical analysis will require a protocol amendment only if it substantively alters the principal features of the protocol. Any deviations from the planned statistical analyses in the protocol will be fully described in the SAP and PAP.

11.3 Analysis Sets

The randomized analysis set will include all subjects who signed the ICF and were randomized into the study.
The safety analysis set will include all subjects who signed the ICF and received at least one dose of study medication.
The mITT analysis set will include all subjects in the randomized analysis set who received at least one dose of study medication. The mITT analysis set will be used for primary and secondary efficacy analyses.
The PPS will include all subjects in the randomized analysis set who received at least one dose of study medication, and who were sufficiently compliant with the protocol, according to pre-specified criteria that will be finalized prior to database lock. The PPS will be used for sensitivity analyses.

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

11.4 Study Population Data

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

11.5 Efficacy Analyses

11.5.1 Primary Efficacy Analyses

The primary efficacy analysis will be performed using the mITT analysis set.
Observed ADPS and change from baseline will be summarized by treatment and week (including Week 14/LOCF and Week 14/baseline observation carried forward [BOCF]).

Mean change from baseline in ADPS will be compared between each DS-5565 arm and placebo at Week 14 using the following multiple imputation (MI) method and mixed-effect model for repeated measurements (MMRM)[17,18] according to the pre-specified test procedure described later in this section.
The primary imputation will be based on "nonfuture dependence" model [19 - 21] using the pattern mixture approach with shifting parameters under the MNAR mechanism for the missing weekly ADPS data. Reason for dropout together with the time of dropout will be used for constructing the missing data pattern. The statistical model used for the MI data generation will be the Markov Chain Monte Carlo (MCMC) method with adjustment for covariates (eg, treatment group, age, sex) to produce a monotone pattern first, and then the imputation will continue using the Regression with Predictive Mean Matching (REGPMM) method for the monotone pattern with the same set of covariates. The imputed value will be set as 10 (the maximal ADPS score) when the imputed value of ADPS score is over 10. Additionally, for dropouts due to LOE, the imputed values will be bound so that a subject's imputed weekly ADPS after discontinuation cannot be better than that subject's baseline ADPS. Each complete imputed dataset will be analyzed using the MMRM with treatment, week, treatment-by-week as the fixed effects, week as the repeated measure, and baseline ADPS as the covariate. The results of MMRM analysis from each complete imputed dataset will be combined using Rubin's rule. All reasons for discontinuation will be categorized, to the extent possible, into either LOE or AE based on detail specified in the Case Report Form. Only reasons that cannot be classified into the above two categories will be considered as "all other reasons (AOR)". The primary shifting parameter values corresponding to the three categories in the pattern mixture model (PMM) will be chosen as (1.0, 1.0, 0.5) for dropouts due to AE, LOE and AOR, respectively, and the corresponding shifting amount of the weekly ADPS imputed at first missing week is given by (1.0, 1.0, 0.5)*RSD*U(0,1) where U(0,1) is a random variable from a uniform distribution with a range of 0 to 1, and RSD is the residual standard deviation at first missing week after imputation.

The type I error rate will be controlled at less than 0.05 for the multiple comparisons of the primary efficacy analyses in the following multiple test procedure.

1) DS-5565 10 mg BID and 15 mg BID will be tested against placebo using Bonferroni-Holm method at significance level of 0.05.
2) The following statistical test will be performed according to the result of 1).
    - If both of arms are statistically significant, DS-5565 15 mg QD arm will be

tested at level of 0.05.

- If neither of the arms is statistically significant, DS-5565 15 mg QD arm will not be tested.
- If either DS-5565 10 mg BID or DS-5565 15 mg BID is statistically significant, DS-5565 15 mg QD arm will be tested at level of 0.025.

Sensitivity analyses will include following:

- The above primary "nonfuture dependence" MNAR model with different shift parameters including (0, 0, 0)
- Placebo multiple imputation[17,18]
- MMRM using observed data only
- ANCOVA using BOCF
- ANCOVA using LOCF
- The above primary "nonfuture dependence" MNAR model with the same shift parameters as the primary analysis (i.e., (1.0, 1.0, 0.5) using PPS).

11.5.2 Secondary Efficacy Analyses

Secondary efficacy analyses will be performed using the mITT analysis set. For all secondary endpoints, the summary statistics or frequency tables will be created by treatment group for each week or scheduled visit. The secondary endpoints for each DS-5565 arm will be compared with that for placebo with no adjustment of multiple comparisons.

11.5.2.1 Responder Rate for Averaged Daily Pain Score

ADPS responder rate, defined as the proportion of subjects with ≥ 30% , and ≥ 50% reduction from baseline to Week 14, will be calculated by treatment group. ADPS responder rate of each arm of DS-5565 will be compared with that of placebo using logistic regression model. The cumulative distribution of reduction from baseline in ADPS will be provided as a continuous responder analysis[15].

11.5.2.2 Short-Form McGill Pain Questionnaire

For the sensory score, affective score, total score, VAS, and the present pain intensity index, the measured value and the change from baseline will be summarized at each scheduled visit. The change from baseline in the parameters above will be compared between each arm of DS-5565 and placebo.

11.5.2.3 Modified Brief Pain Inventory (Short Form)

For the parameters related to severity of pain and impact on daily functions, the measured value and the change from baseline will be summarized at each scheduled visit. The change from baseline in the parameters above will be compared between each arm of DS-5565 and placebo.

11.5.2.4 Patient Global Impression of Change

PGIC score (1 to 7 on a 7-point scale) will be described as frequency table and will be compared between each arm of DS-5565 and placebo.

11.5.2.5 Sleep-Interference Score

The summary statistics will be computed for the ADSIS and their change from baseline at each week. The change from baseline in sleep interference score will be compared between each arm of DS-5565 and placebo.

11.5.2.6 Medical Outcomes Study Sleep Scale

For the subscales of sleep disturbance, snoring, awakening short of breath or with a headache, somnolence, sleep adequacy, sleep problems index, and quantity of sleep, the measured value and the change from baseline will be summarized at each scheduled visit. The change from baseline in the subscales above will be compared between each arm of DS-5565 and placebo.

For the optimal sleep which is dichotomized version of optimal sleep findings, the summary will be provided as frequency tables and the parameter will be compared between treatments.

11.5.2.7 Hospital Anxiety and Depression Scale

For the subscales of anxiety and depression, the measured value and the change from baseline will be summarized at baseline and Visit 10. The change from baseline in the subscales above will be compared between each arm of DS-5565 and placebo.

11.5.2.8 SF-36

For the eight-scale profile of physical functioning, role-physical, bodily pain, general perception of health, vitality, social functioning, role-emotional, and mental health, the transformed score and their change from baseline will be described as summary statistics

at each scheduled visit. The change from baseline will be compared between each arm of DS-5565 and placebo for each scale profile above.

11.5.2.9 Evaluation of Symptoms

The evaluation of symptoms (four categories of "improved", "no change", "worse", "no symptoms") will be described as frequency table and will be compared between each arm of DS-5565 and placebo.

11.6 Pharmacokinetic/Biomarker Analyses

11.6.1 Pharmacokinetic Analyses

Scatter plot illustrating the pharmacokinetic relationship between time after dose and plasma concentration by treatment for each visit will be created, using the PK analysis set. The population PK analysis will be reported separately from the clinical study report (i.e. not in the clinical study report).

11.6.2 Biomarker Analyses

Not applicable.

11.7 Safety Analyses

All safety analyses will be performed on a by-treatment basis, unless otherwise specified, using the safety analysis set.

11.7.1 Adverse Event Analyses

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

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

- TEAE
- ADR
- Serious TEAE
- Serious ADR

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

Time to first TEAE, defined as the duration from first administration of investigational product to the first TEAE, will be summarized based on the Kaplan-Meier product limit method by treatment and all-DS-5565 treatment.

11.7.2 Clinical Laboratory Evaluation Analyses

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

Additionally, for ALT, AST, T-Bil, and ALP, the number and percentage of subjects who meet the criteria specified in Food Drug Administration (FDA) Drug-Induced Liver Injury (DILI) guideline[16] and evaluation of drug-induced serious hepatotoxicity (e-DISH) plot will be provided. For the urinalysis parameters excepting specific gravity, the number and percentage of subjects will be provided at each visit. Summary statistics will be tabulated for the specific gravity. A shift table will be created based on the categories of "normal" and "abnormal" between baseline and each scheduled visit.

11.7.3 Vital Sign Analyses

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

11.7.4 Electrocardiogram Analyses

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

11.7.5 Physical Finding Analyses

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

or absence) will be tabulated for each expression site.

11.7.6 Columbia-Suicide Severity Rating Scale

The data collected from C-SSRS will be tabulated.

11.7.7 Hospital Anxiety and Depression Scale

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

11.7.8 Other Safety Analyses

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

11.8 Other Analyses

Not applicable.

11.9 Data Safety Monitoring Board

An independent DSMB will be responsible for reviewing unblinded safety data in an ongoing manner and for monitoring and assuring overall safety of the study subjects. In accordance with an agreed-upon charter, the DSMB will meet periodically, on a regular and/or ad hoc basis, to discuss and address any emerging safety or tolerability issues, including SAEs, discontinuations due to AEs, etc, as well as other relevant study information, such as recruitment status, ineligibility rates, and data quality. Based on any formal DSMB review meeting where blinded or unblinded safety data are reviewed and discussed, the DSMB will recommend to the sponsor one of the following:

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

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

- Concern about drug-induced liver injury
- Concern about suicide

- Any other safety concern

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

The 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. The HAC will adjudicate hepatic events in a blinded manner. This adjudication will be independent of the investigators. The HAC will complete assessments on an ongoing basis. Adjudication of hepatic events will be based on evaluation of eCRFs and source documents, as available, including but not limited to hospital discharge summaries, diagnostic imaging, histopathology, consultation, and laboratory reports. Such patient's relevant records will be provided to the HAC from the study sites according to HAC request.

11.11 Sample Size Determination

Approximately 750 subjects will be randomized to one of placebo (300 subjects), DS-5565 15 mg QD (150 subjects), DS-5565 10 mg BID (150 subjects), or DS-5565 15 mg BID (150 subjects) according to the randomization ratio of 2:1:1:1.

This sample size provides around 90% statistical power which is the probability of DS-5565 15 mg BID (or DS-5565 10 mg BID) superiority over the placebo under the assumption of 0.6 difference (vs placebo) in change from baseline in ADPS (ΔADPS) for all DS-5565 arms and common SD for ΔADPS of 1.8 units. The statistical power is based on Analysis of Variance (ANOVA) using combination approach of Bonferroni-Holm method and gate-keeping procedure (see Section 11.5.1) to control the type I error rate at less than 0.05. The statistical power shown in Table 11-1 is simulation-basis (100,000 repetitions).

Table 11-1 Statistical powers (%) of DS-5565 15 mg QD, 10 mg BID, and 15 mg BID being superior over placebo

Difference (15 mg QD, 10 mg BID, 15 mg BID) and SD	15 mg QD	10 mg BID	15 mg BID
Diff=(0.6, 0.6, 0.6), SD=1.8	87.0%	89.5%	89.3%
Diff=(0.4, 0.6, 0.6), SD=1.8	56.9%	87.7%	87.5%

12. DATA INTEGRITY AND QUALITY ASSURANCE

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

12.1 Monitoring and Inspections

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

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

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

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

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

12.2 Data Collection

12.2.1 Style of Data Collection

12.2.1.1 Case Report Form

This study will use an Electronic Data Capture (EDC) system (Table 12-1) to generate CRFs, so the CRFs will be entered electronically. CRFs (including audit trails) will be prepared for each subject. The eCRF will be completed, reviewed, and e-signed by the investigators. The EDC system will be validated prior to use.

Table 12-1 Electronic Data Capture System

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

12.2.1.2 Electronic Daily Diary

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

Table 12-2 Electronic Patient Report Outcome System

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

12.2.1.3 Other Reports

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

12.2.2 Preparation of Case Report Forms and Daily Diaries

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

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

12.2.3 Signatures or Seals on the Case Report Form

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

12.2.4 Data Correction

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

12.3 Data Management

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

To ensure the quality of clinical data across all subjects and study sites, a Clinical Data Management review will be performed on subject data according to specifications given to Daiichi Sankyo. Data will be vetted electronically and/or manually as appropriate. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, data will be reviewed for adherence to the protocol and GCP. For eCRFs and ePRO data will be electronically vetted by programmed data rules within the application. Queries generated by rules and raised by reviewers will be generated within the EDC or ePRO applications and also resolved within the applications.

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

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

All AEs will be coded using MedDRA.

12.4 Study Documentation and Storage

12.4.1 Definition of Source Documents

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

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

1) Direct entry of specific items (in the Comments column, etc.)
2) Entries such as "None" or "Unknown" for specific items
3) Reasons for use of concomitant drugs
4) Laboratory values that deviated from the reference range, if any, and reason for deviation.

5) Descriptions of AEs
6) AEs, if any, name of AE, severity, seriousness, outcome, relationship to the investigational product
7) Whether treatment was discontinued, and reason for discontinuation

12.4.2 Storage

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

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

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

12.5 Record Keeping

Records of subjects, source documents including electronic daily diary, monitoring visit logs, data correction forms, CRFs, inventory of investigational product, regulatory documents (eg, protocol and amendments, IRB/EC correspondence and approvals, approved and signed ICFs, Investigator's Agreement, clinical supplies receipts, distribution and return records), and other sponsor correspondence pertaining to the study must be kept in appropriate study files at the study site.

13. FINANCING AND INSURANCE

13.1 Finances

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

13.2 Reimbursement, Indemnity, and Insurance

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

14. PUBLICATION POLICY

[redacted]

15. STUDY ADMINISTRATIVE INFORMATION

15.1 Compliance Statement, Ethics, and Regulatory Compliance

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

15.2 Subject Confidentiality

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

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

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

15.3 Informed Consent Procedures

Before a subject's participation in the study, it is the investigator's responsibility to obtain freely given consent, in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific procedures or any investigational products are administered. The written ICF should be prepared in the local language(s) of the potential subject population.

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

subjects.

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

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

15.4 Regulatory Compliance

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

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

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

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

documents are implemented only after approval by the relevant regulatory bodies.

15.5 Protocol Deviations

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

A deviation to eliminate an apparent immediate hazard to one or more subjects may be implemented immediately. The sponsor and the IRB/EC must be notified.
The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

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

15.6 Supply of New Information Affecting the Conduct of the Study

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

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

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

15.7 Duration of the Study

Study duration: January 2015 to May 2017

15.8 Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be communicated to the investigator by Daiichi Sankyo. Also, the sponsor will assure the timely submission of amendments to regulatory authorities.

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

A local protocol amendment will affect study conduct at a particular study site(s) and/or in a particular region/country. Such amendments generally will not be incorporated into a revised protocol document. Changes made by such amendments will be clearly stated in a document separate from the protocol. Sponsor approval of local amendments will be clearly documented.

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

15.9 Study Discontinuation or Suspension

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

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

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

If the sponsor decides to prematurely terminate part of the study or the entire study after

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

15.10 Organization

15.10.1 Sponsor

15.10.1.1 Sponsor's Responsible Medical Expert

PPD

PPD

PPD

PPD

15.10.1.2 Sponsor's Responsible Medical Adviser

PPD

PPD

PPD

PPD

15.10.1.3 Sponsor's Clinical Study Lead

PPD

Clinical Development Department, R&D Division, Daiichi Sankyo Co., Ltd.
1-2-58, Hiromachi, Shinagawa-ku, Tokyo, 140-8710, Japan

PPD

PPD

15.10.1.4 Sponsor's Delivery Lead

PPD

Clinical Development Department, R&D Division, Daiichi Sankyo Co., Ltd.
1-2-58, Hiromachi, Shinagawa-ku, Tokyo, 140-8710, Japan

PPD

PPD

PPD

Asia Development Department, R&D Division, Daiichi Sankyo Co., Ltd.
1-2-58, Hiromachi, Shinagawa-ku, Tokyo, 140-8710, Japan

PPD

PPD

15.10.2 Academic Research Organization

Not applicable

15.10.3 Coordinating Investigator

15.10.3.1 Coordinating Investigator in Japan

PPD

PPD

PPD

PPD

15.10.3.2 Coordinating Investigator in Korea

PPD

PPD

PPD

PPD

15.10.3.3 Coordinating Investigator in Taiwan

PPD

PPD

PPD

PPD

15.10.4 Contract Research Organization

15.10.4.1 Contract Research Organization in Charge of Monitoring in Japan

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

PPD

PPD

15.10.4.2 Contract Research Organization in Charge of Monitoring in Korea

Quintiles Transnational Korea Co., Ltd.

13th Floor, World Tower Building, 558 Songpa-daero, Songpa-gu, Seoul, Korea, 138-731

PPD

PPD

15.10.4.3 Contract Research Organization in Charge of Monitoring in Taiwan

Quintiles Taiwan Ltd.

8F, No. 134, Sec. 3, Min Sheng East Road, Taipei, 105, Taiwan, R.O.C.

PPD

PPD

15.10.4.4 Contract Research Organization in Charge of Monitoring in Malaysia

Quintiles Malaysia Sdn. Bhd.

Suite D-08-02 Plaza Mont Kiara, No. 2 Jalan Kiara, Mont Kiara, 50480 Kuala Lumpur, MALAYSIA

PPD

PPD

15.10.4.5 Contract Research Organization in Charge of Interactive Web Response System

PPD

Bell Medical Solutions. Inc.

Tokyu Bldg. East No.3, 2-16-8 Minami-Ikebukuro, Toshima-ku, Tokyo, 171-0022, Japan

PPD

PPD

PPD

PPD

15.10.4.6 Contract Research Organization in Charge of Emergency Contact

Bell Medical Solutions. Inc.

Tokyu Bldg. East No.3, 2-16-8 Minami-Ikebukuro, Toshima-ku, Tokyo, 171-0022, Japan

PPD

PPD

15.10.4.7 Randomization manager

PPD

Bell Medical Solutions. Inc.

Tokyu Bldg. East No.3, 2-16-8, Minami-Ikebukuro, Toshima-ku, Tokyo, 171-0022, Japan

PPD

PPD

15.10.5 Central Laboratory

15.10.5.1 Bioanalytical Laboratory

Celerion

621 Rose Street, Lincoln, NE 68502 USA

PPD

PPD

15.10.5.2 Central Laboratory Management

SRL Medisearch Inc.

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

PPD

PPD

15.10.5.3 Central Laboratory in Japan

SRL, Inc.

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

PPD

PPD

15.10.5.4 Central Laboratory Management in Korea

Meditree Co., Ltd.

#501, 38-3, Baumoero 41-gil, Seocho-gu, Seoul, 137-886, Korea

PPD

PPD

15.10.5.5 Central Laboratory in Korea

Samkwang Medical Laboratories

#9-60 Yangjae-dong, Seocho-gu, Seoul 137-887, Korea

PPD

PPD

15.10.5.6 Central Laboratory in Taiwan

Protech Pharmaservices Corporation

11F. No.3, Park St., Nangang District, Taipei City 11503, Taiwan

PPD

PPD

15.10.5.7 Central Laboratory in Singapore

Eurofins Medinet Pte Ltd

1 International Business Park, #01-16 The Synergy, Singapore 609917

PPD

PPD

15.10.6 Data Safety Monitoring Board

PPD

PPD

PPD

PPD

PPD

PPD

PPD

PPD

PPD

PPD

PPD

PPD

PPD

PPD

PPD

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

MMS Holdings, Inc.

6880 Commerce Blvd, Canton, MI 48187, USA

PPD

PPD

15.10.8 Hepatic Adjudication Committee

PPD

PPD

PPD

15.10.9 Contract Research Organization in Charge of Hepatic Adjudication Committee Coordination

MMS Holdings, Inc.

6880 Commerce Blvd, Canton, MI 48187, USA

PPD

PPD

15.10.10 EDC System Development

Medidata Solutions, Inc.

Person Responsible: Tarek Sherif, Chairman and Chief Executive Officer

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

PPD

PPD

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

15.10.11 EDC System Support

Fujitsu Systems East Limited

Person Responsible: Manabu Yamamoto

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

Japan

PPD

PPD

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

15.10.12 ePRO system Development and Support

eResearchTechnology, Inc

Person Responsible: Satoshi Azuta

PPD

PPD

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

16. REFERENCES

1) Li CY, Zhang XL, Matthews EA, et al. Calcium channel $\alpha_2\delta_1$ subunit mediates spinal hyperexcitability in pain modulation. Pain. 2006;125(1-2):20-34.
2) Taylor CP. Mechanisms of analgesia by gabapentin and pregabalin – Calcium channel α_2-δ [$Ca_v\alpha_2$-δ] ligands. Pain. 2009;142(1-2):13-6.
3) Field MJ, Li Z, Schwartz JB. Ca^{2+} channel α_2-δ ligands for the treatment of neuropathic pain. J Med Chem. 2007;50(11):2569-75.
4) Field MJ, Cox PJ, Stott E, et al. Identification of the α_2-δ-1 subunit of voltage-dependent calcium channels as a molecular target for pain mediating the analgesic actions of pregabalin. Proc Natl Acad Sci USA. 2006;103(46):17537-42.
5) European Medicines Agency (EMEA), Committee for Medicinal Products for Human Use (CHMP), Guideline on Clinical Medicinal Products Intended for the Treatment of Neuropathic Pain. July, 2007.
6) Satoh J, Yagihashi S, Baba M. Efficacy and safety of pregabalin for treating neuropathic pain associated with diabetic peripheral neuropathy: a 14 week, randomized, double-blind, placebo-controlled trial. Diab Med. 2011;28(1):109-16.
7) Farrar JT, Young JP Jr, LaMoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain. 2001;94(2):149-58.
8) Melzack R. The Short-Form McGill Pain Questionnaire. Pain. 1987;30(2):191-7.
9) Zelman DC, Gore M, Dukes E, et al. Validation of a modified version of the Brief Pain Inventory for painful diabetic peripheral neuropathy. J Vasc Nurs 2005; 23(3):97-104
10) Viala-Danten M, Martin S, Guillemin I, et al. Evaluation of the reliability and validity of the Medical Outcome Study sleep scale in patients with painful diabetic peripheral neuropathy during an international clinical trial. Health Qual Life Outcomes 2008;6:113-25
11) Hays RD, Stewart AL. Sleep measures. In: Measuring Functioning and Well-Being. Stewart AL, Ware JE Jr editors. Durham and London: Duke University Press; 1992;235-259.
12) Bjelland I, Dahl AA, Haug TT, et al. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res. 2002;52(2):69-77.
13) Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. Med Care 1992;30(6):473-83.

14) Oquendo MA, Halberstam B, Mann JJ. Risk factors for suicidal behavior: utility and limitations of research instruments. In: First MB, editor. Standardized Evaluation in Clinical Practice Arlington: American Psychiatric Publishing, Inc; 2003;103-130.
15) Kim Y. Missing data handling in chronic pain trials, J Biopharm Stat. 2011;21(2):311-25.
16) U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Center for Biologics Evaluation and Research (CBER). Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation. July 2009, Drug Safety
17) Mallinckrodt CH, Lin Q, Lipkovich, et al. A structured approach to choosing estimands and estimators in longitudinal clinical trials. Pharm Stat, 2012;11(6):456-61
18) Mallinckrodt CH, Lin Q, Molenberghs G. A structured framework for assessing sensitivity tomissing data assumptions in longitudinal clinical trials. Pharm Stat, 2013;12(1):1-6
19) National Academy of Science. The Prevention and Treatment of Missing Data in Clinical Trials. Washington: National Academies Press;2010
20) Little RJ, D'Agostino R, Cohen ML, et al. The Prevention and Treatment of Missing Data in Clinical Trials. N Eng J Med 2012;367(14):1355-60
21) Kenward MG, Molenberghs G, Thijs H. Pattern mixture models with proper time dependence. Biometrika. 2003;90(1):53-71.

17. APPENDICES

17.1 Schedule of Events

Table 17-1 Study Visits

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

CLINICAL STUDY PROTOCOL

AN ASIAN, PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED 14-WEEK STUDY OF DS-5565 IN PATIENTS WITH DIABETIC PERIPHERAL NEUROPATHIC PAIN FOLLOWED BY A 52-WEEK OPEN-LABEL EXTENSION

-For Open-Label Extension study-

DS5565-A-J303

VERSION 6.0, 18 Apr 2016

DAIICHI SANKYO

IMPORTANT STUDY ADMINISTRATIVE INFORMATION

Sponsor	Daiichi Sankyo Co., Ltd. 3-5-1, Nihonbashi-honcho, Chuo-ku, Tokyo 103-8426, Japan TEL: see Section 15.10 FAX: see Section 15.10
Contract Research Organization (Japan):	CMIC Co., Ltd. 1-1-1, Shibaura, Minato-ku, Tokyo, 105-0023, Japan PPD PPD
Contract Research Organization (Korea):	Quintiles Transnational Korea Co., Ltd. 13th Floor, World Tower Building, 558 Songpa-daero, Songpa-gu, Seoul, Korea 138-731 PPD PPD
Contract Research Organization (Taiwan):	Quintiles Taiwan Ltd. 8F, No. 134, Sec. 3, Min Sheng East Road, Taipei, 105, Taiwan, R.O.C. PPD PPD

PROTOCOL SYNOPSIS

Protocol Number:	DS5565-A-J303
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 Asian, phase 3, multicenter, randomized, double-blind, placebo-controlled 14-week study of DS-5565 in patients with diabetic peripheral neuropathic pain (DPNP) followed by a 52-week open-label extension
Study Phase:	Phase 3
Indication Under Investigation:	DPNP
Study Objectives:	To assess the long-term safety and efficacy of DS-5565 for a flexible dosing of 10 mg BID and 15 mg BID in subjects with DPNP
Study Design:	Open-label, long-term study The study duration is approximately 53 weeks, including a treatment period of 52 weeks with a follow-up period of 1 week. After the treatment period of the double-blind study, the first 2 weeks will be the titration period with administration of 5 mg BID. For the second 2 weeks, the investigational product is administered at a dosage of 10 mg BID. From the fifth week, if there are no concerns in safety, administration will be increased to 15 mg BID. For the following visits, the dosage may change to either 10 mg BID or 15 mg BID depending on safety findings.
Study Duration (from FPI to LPLV):	Study duration: January 2015 to May 2017
Study Sites and Location:	Approximately 200 study sites in Japan, Korea and Taiwan
Planned Sample Size:	Approximately 400 subjects will be enrolled in the study.
Subject Eligibility Criteria:	Inclusion Criteria: Subjects must satisfy all of the following criteria to be included in the study. 1) Completed 14 weeks of administration in the double-blind study 2) Able to give written informed consent for study participation, understand procedures of this study, and complete patient-reported questionnaires adequately Exclusion Criteria: Subjects who meet any of the following criteria will be excluded from participation in the study. 1) Drug compliance < 80% in the double-blind study

	2) Creatinine clearance (using the Cockcroft-Gault equation) < 60 mL/min at Visit 9 of the double-blind study 3) Experienced critical safety issue in the double-blind study 4) Known history of positive Hepatitis B antigen or Hepatitis C antibody 5) Previous treatment with drugs that could cause irreversible retinal degeneration 6) Pregnancy, potential pregnancy, breast feeding, or subject unwilling to take reliable contraceptive measures during the study or for 4 weeks after study completion 7) The subject is considered inappropriate for the study at the discretion of the investigator or sub-investigator
Dosage Form, Dose, and Route of Administration:	DS-5565 is administered orally twice daily. The first 2 weeks of the titration period, the investigational product is administered at a dosage of 5 mg BID. For the second 2 weeks, the dosage will be 10 mg BID. From the fifth week, if there are no concerns in safety, administration will be increased to 15 mg BID. For the following visits, the dosage may change to either 10 mg BID or 15 mg BID depending on safety findings at the time of each visit.
Study Endpoints:	Safety: • Adverse Events (AEs) • clinical laboratory evaluations • vital sign • 12-lead electrocardiogram (ECG) • body weight • physical examinations • edema • neurological examinations • ophthalmologic examination • Columbia-Suicide Severity Rating Scale (C-SSRS) • Hospital Anxiety and Depression Scale (HADS) Efficacy: • Short-Form McGill Pain Questionnaire (SF-MPQ)
Statistical Analyses:	The safety analysis set will be used for all safety analyses and efficacy analyses. AEs, clinical laboratory test results, vital signs (including body weight), 12-lead-ECGs, physical findings, C-SSRS and HADS will be summarized. Efficacy endpoints will be described as summary statistics.

TABLE OF CONTENTS

IMPORTANT STUDY ADMINISTRATIVE INFORMATION 2
PROTOCOL SYNOPSIS 3
TABLE OF CONTENTS 5
LIST OF IN-TEXT TABLES 9
LIST OF ABBREVIATIONS 10
1. INTRODUCTION AND BACKGROUND INFORMATION 12
1.1 Data Summary 12
1.2 Study Rationale 12
1.3 Risks and Benefits for Study Subjects 12
2. STUDY OBJECTIVES AND HYPOTHESES 13
2.1 Study Objectives 13
2.2 Study Hypothesis 13
3. STUDY DESIGN 14
3.1 Overall Plan 14
3.1.1 Study Type 14
3.1.2 Study Scheme 14
3.1.3 Study Endpoints 14
3.1.3.1 Safety 14
3.1.3.2 Efficacy 15
3.1.4 Duration of Subject Participation 15
3.2 Discussion of Study Design 15
4. STUDY POPULATION 16
4.1 Enrollment 16
4.1.1 Procedures for Subject Enrollment 16
4.1.2 Inclusion Criteria 16
4.1.3 Exclusion Criteria 16
4.2 Subject Withdrawal 17
4.2.1 Withdrawal Criteria 17
4.2.2 Reasons for Withdrawal 17
4.2.3 Withdrawal Procedures 18
4.2.4 Stopping Rules for the Study 18
5. TREATMENT ADMINISTERED 19
5.1 Investigational Products 19
5.1.1 Study Treatments 19

5.1.1.1 Investigational Product 19
5.1.2 Dosing Regimens for the Study 19
5.1.3 Method of Assessing Treatment Compliance 19
5.1.4 Labeling and Packaging 20
5.1.5 Storage 20
5.1.6 Drug Accountability 20
5.2 Concomitant Medications and Treatments 20
5.2.1 Prohibited Concomitant Medications 20
5.2.2 Other 21
6. STUDY PROCEDURES 22
6.1 Visit 10 22
6.2 Visit 11 22
6.3 Visit 12 23
6.4 Visit 13 to Visit 23 24
6.5 End of Treatment/Early Termination (Visit 24) 24
6.6 Post-treatment Follow-up (Visit 25, 7 days after the completion of administration) 25
7. EFFICACY ASSESSMENTS 26
8. PHARMACOKINETIC AND BIOMARKER ASSESSMENTS 27
8.1 Pharmacokinetic Variable(s) 27
8.2 Biomarker Variable(s) 27
9. SAFETY ASSESSMENTS 28
9.1 Adverse Events 28
9.1.1 Definition of Adverse Event 28
9.1.2 Items to Be Investigated Concerning Adverse Events 29
9.1.3 Definition of Adverse Drug Reaction 31
9.1.4 Actions to Be Taken When Adverse Events Occur 31
9.2 Actions to Be Taken When Serious Adverse Events Occur 32
9.3 Exposure In Utero During Clinical Studies 32
9.4 Clinical Laboratory Evaluations 33
9.5 Vital Signs 37
9.6 Electrocardiograms 37
9.7 Physical Findings 37
9.7.1 Body Weight 37
9.7.2 Physical Examinations 37
9.7.3 Evaluation of Edema 37

9.8 Other Safety Assessments 37
9.8.1 Neurological Examination 37
9.8.2 Ophthalmologic Examination 38
9.8.3 Columbia-Suicide Severity Rating Scale[24] 38
9.8.4 Hospital Anxiety and Depression Scale[22] 38
9.8.5 Pregnancy test 39
10. OTHER ASSESSMENTS 40
11. STATISTICAL METHODS 41
11.1 Objective 41
11.2 General Statistical Considerations 41
11.3 Analysis Sets 41
11.4 Study Population Data 42
11.5 Efficacy Analyses 42
11.6 Pharmacokinetic/Biomarker Analyses 42
11.7 Safety Analyses 42
11.7.1 Adverse Event Analyses 42
11.7.2 Clinical Laboratory Evaluation Analyses 43
11.7.3 Vital Sign Analyses 43
11.7.4 Electrocardiogram Analyses 43
11.7.5 Physical Finding Analyses 43
11.7.6 Columbia-suicide Severity Rating Scale 43
11.7.7 Hospital Anxiety and Depression Scale 43
11.7.8 Other Safety Analyses 43
11.8 Other Analyses 44
11.9 Data Safety Monitoring Board 44
11.10 Hepatic Adjudication Committee 44
11.11 Sample Size Determination 44
12. DATA INTEGRITY AND QUALITY ASSURANCE 45
12.1 Monitoring and Inspections 45
12.2 Data Collection 45
12.3 Data Management 45
12.4 Study Documentation and Storage 45
12.5 Record Keeping 45
13. FINANCING AND INSURANCE 46
13.1 Finances 46

13.2 Reimbursement, Indemnity, and Insurance 46
14. PUBLICATION POLICY 47
15. STUDY ADMINISTRATIVE INFORMATION 48
15.1 Compliance Statement, Ethics, and Regulatory Compliance 48
15.2 Subject Confidentiality 48
15.3 Informed Consent Procedures 48
15.4 Regulatory Compliance 48
15.5 Protocol Deviations 48
15.6 Supply of New Information Affecting the Conduct of the Study 48
15.7 Duration of the Study 48
15.8 Protocol Amendments 48
15.9 Study Discontinuation or Suspension 48
15.10 Organization 48
16. REFERENCES 49
17. APPENDICES 50
17.1 Schedule of Events 50

LIST OF IN-TEXT TABLES

Table 9-1 Items to be Investigated for Adverse Event 30
Table 9-2 Laboratory Parameters to be Assessed, and Time of Assessment..... 34
Table 17-1 Study Visits 50

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ADR	Adverse Drug Reaction
AE	Adverse Event
A/G ratio	Albumin/Globulin ratio
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AMA	anti-mitochondrial antibody
ANA	anti-nuclear antibody
ASMA	anti-smooth muscle antibody
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CMV	Cytomegalovirus
CNS	Central Nervous System
CRF	Case Report Form
CRP	C-Reactive Protein
C-SSRS	Columbia-Suicide Severity Rating Scale
DILI	Drug-Induced Liver Injury
DSMB	Data Safety Monitoring Board
DPN	Diabetic Peripheral Neuropathy
DPNP	Diabetic Peripheral Neuropathic Pain
EBV	Epstein-Barr Virus
eCRF	Electronic Case Report Form
EC	Independent Ethics Committee
ECG	Electrocardiogram
e-DISH	Evaluation of Drug-Induced Serious Hepatotoxicity
EIU	Exposure In Utero
ePRO	Electronic Patient Report Outcome
FDA	Food Drug Administration
FPI	First Patient In
GCP	Good Clinical Practice (refers to ICH and CFR)
γ-GT(γ-GTP)	gamma-Glutamyl Transpeptidase
GOT	Glutamic Oxaloacetic Transaminase
GPT	Glutamic Pyruvic Transaminase
HAC	Hepatic Adjudication Committee
HADS	Hospital Anxiety and Depression Scale
ICF	Informed Consent Form

ABBREVIATION	DEFINITION
ICH	International Conference on Harmonization
INN	International Non-proprietary Name
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LOE	Lack of Efficacy
LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
NASH	Nonalcoholic Steatohepatitis
PT	Prothrombin Time
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SF-MPQ	Short-Form McGill Pain Questionnaire
TEAE	Treatment-Emergent Adverse Event
T-Bil	Total bilirubin
ULN	Upper Limit of Normal
VAS	Visual Analog Scale
WBC	White Blood Cell

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1 Data Summary

Refer to Section 1.1 of double-blind study in the protocol (DS5565-A-J303).

1.2 Study Rationale

Currently available $\alpha_2\delta$ ligands, gabapentin and pregabalin, are established as effective first-line treatments for pain associated with diabetic peripheral neuropathy (DPN).[2,3] However, the dosage, and thus efficacy, of these agents is limited by frequent and significant central nervous system (CNS)-related side effects, including dizziness and somnolence; associated weight gain and peripheral edema can also be problematic. As a result, a large proportion of patients with diabetic peripheral neuropathic pain (DPNP) are left with insufficient pain relief, and new treatment options are needed.

DS-5565 is an oral analgesic drug being developed for DPNP and other indications. DS-5565 is an antagonist to the $\alpha_2\delta$ subunit of voltage-dependent Ca^{2+} channels, the main target molecule for the analgesic effect of pregabalin and gabapentin. Nonclinical (Section 1.1.1.4 of double-blind study in the protocol [DS5565-A-J303]) and clinical (Section 1.1.1.5 of double-blind study in the protocol [DS5565-A-J303]) data support the progress of DS-5565 into Phase 3 studies in DPNP.

DS-5565 is being developed for chronic use in DPNP and other indications. Therefore, this long-term study will be conducted to evaluate the long-term safety and efficacy of DS-5565 during the course of a 52 week (including titration period) open treatment period.

1.3 Risks and Benefits for Study Subjects

Refer to Section 1.3 of double-blind study in the protocol (DS5565-A-J303).

2. STUDY OBJECTIVES AND HYPOTHESES

2.1 Study Objectives

The objective is to assess the long-term safety and efficacy of DS-5565 for a flexible dosing of 10 mg BID and 15 mg BID in subjects with DPNP.

2.2 Study Hypothesis

The hypothesis of the long-term study is that DS-5565 will be generally well tolerated when administered with a flexible dosing of 10 mg BID and 15 mg BID for up to 52 weeks.

3. STUDY DESIGN

3.1 Overall Plan

3.1.1 Study Type

This is a multinational, open-label, long-term study for treatment of DPNP.

Study sites: Approximately 200 study sites in Japan, Korea and Taiwan.
Planned sample size is approximately 400 subjects who will be enrolled in the study.

3.1.2 Study Scheme

The total study duration is approximately 53 weeks, including a treatment period of 52 weeks with a follow-up period of 1 week. After the treatment period of the double-blind study, the first 2 weeks will be the titration period with administration of 5 mg BID. For the second 2 weeks, the investigational product is administered at a dose of 10 mg BID. From the fifth week, if there are no concerns in safety, administration will be increased to 15 mg BID. For the following visits, the dosage may change to either 10 mg BID or 15 mg BID depending on safety findings at the time of each visit.

On evaluation of risk and benefit by the sponsor, if it is not the positive result as compared with placebo arm in 10 mg BID arm or 15 mg BID arm of DS-5565 of double-blind study in the protocol (DS5565-A-J303), the dosage in this study will be changed to the optimal dose of DS-5565.

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

3.1.3 Study Endpoints

3.1.3.1 Safety

- Adverse Events (AEs)
- clinical laboratory evaluations
- vital sign
- 12-lead electrocardiogram (ECG)
- body weight
- physical examinations
- edema
- neurological examinations

- ophthalmologic examination
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Hospital Anxiety and Depression Scale (HADS)

3.1.3.2 Efficacy

- Short-Form McGill Pain Questionnaire (SF-MPQ)

3.1.4 Duration of Subject Participation

The duration of subject participation will be approximately 53 weeks, including a 2 weeks of titration period, a 50 weeks of dosage adjustment period, and a 1-week follow-up period.

3.2 Discussion of Study Design

In accordance to International Conference on Harmonization (ICH)-E1 guideline, DS-5565 will be administered for 52 weeks to evaluate the long-term safety. It is expected that, in post-marketing, the dose of DS-5565 will be adjusted up or down depending on the patient's symptoms. Therefore, 10 mg BID and 15 mg BID, which are medium and highest dose in the double-blind study, were selected and the dose of DS-5565 will be adjusted in the long-term study. In the Phase 2 studies in patients with DPNP (DS5565-A-U201 and DS5565-A-J202), DS-5565 was generally tolerable at doses of 10 mg BID and 15 mg BID. The lowest dose in the double-blind study (15 mg QD) was not selected. For subject safety, 5 mg BID, which is lower than 10 mg BID or 15 mg BID, was selected as an initial dose of DS-5565 and will be administered for first 2 weeks of the study treatment.

The safety endpoints were selected to evaluate the long-term safety of DS-5565. AEs, clinical laboratory evaluations, physical examinations, ECGs, and vital sign are commonly evaluated for safety assessment in clinical studies. Body weight was selected to evaluate edema, which is a known adverse reaction of DS-5565. Assessments by HADS and C-SSRS were selected to evaluate the risk of anxiety, depression, or suicidal tendency. Neurological examination was selected to evaluate gait/station and muscle strength. In addition, the efficacy of DS-5565 will be also evaluated with SF-MPQ, which can evaluate affective or sensory score, as well as pain intensity.

4. STUDY POPULATION

4.1 Enrollment

Subjects will be considered enrolled upon signature of the Informed Consent Form (ICF) for this study at Visit 10.
Subjects are to be enrolled in this study using the Interactive Web Response System (IWRS) in accordance with the procedures specified below. The identification code will be recorded in a subject identification log.

4.1.1 Procedures for Subject Enrollment

The investigator or sub-investigator will perform a mandatory interview to assess the eligibility of subjects for the study, after obtaining each subject's written informed consent, and will make necessary entries in the IWRS at Visit 10 of the double-blind study.

If the subject is considered ineligible for the study, the investigator or sub-investigator will inform the subject, and follow-up observations will be conducted at Visit 11 of the double-blind study.

4.1.2 Inclusion Criteria

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

1) Completed 14 weeks of administration in the double-blind study
2) Able to give written informed consent for study participation, understand procedures of this study, and complete patient-reported questionnaires adequately

Rationale

1) This criteria was selected to assess appropriately the long-term safety of the investigational product.
2) The study will be conducted in accordance with Good Clinical Practice (GCP).

4.1.3 Exclusion Criteria

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

1) Drug compliance < 80% in the double-blind study
2) Creatinine clearance (using the Cockcroft-Gault equation) < 60 mL/min at Visit 9 of the double-blind study

3) Experienced critical safety issue in the double-blind study
4) Known history of positive Hepatitis B antigen or Hepatitis C antibody
5) Previous treatment with drugs that could cause irreversible retinal degeneration
6) Pregnancy, potential pregnancy, breast feeding, or subject unwilling to take reliable contraceptive measures during the study or for 4 weeks after study completion
7) The subject is considered inappropriate for the study at the discretion of the investigator or sub-investigator

Rationale

1), 2), 3), 4), 5), 6), 7) These criteria were selected so that efficacy and safety could be appropriately assessed in subjects.

4.2 Subject Withdrawal

Refer to Section 4.2 of double-blind study in the protocol (DS5565-A-J303).

4.2.1 Withdrawal Criteria

Refer to Section 4.2.1 of double-blind study in the protocol (DS5565-A-J303).

4.2.2 Reasons for Withdrawal

If a subject discontinues from the study treatment for any reason, the date and the reason for discontinuation must be recorded on the electronic case report form (eCRF) using the following criteria.

- AE
- Death
- Lack of efficacy (LOE)
- Lost to follow-up
- Protocol violation
- Pregnancy
- Study terminated by sponsor
- Withdrawal by subject (eg, AE, LOE, Other)
- Other

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

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

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

All subjects who are withdrawn from the study should complete protocol-specified withdrawal procedures (see Section 4.2.3 and Section 6.5).

4.2.3 Withdrawal Procedures

If the subject withdraws or is withdrawn from the study before the completion of investigational product administration, appropriate measures will be implemented. In addition, to the extent that the subject's cooperation can be obtained, all observations and tests scheduled for the End of Treatment/Early Termination Visit (Visit 24) will be conducted, assessments will be made at that time point, all observations and tests scheduled for the Post-treatment Follow-up Visit (Visit 25) will be conducted, and assessments will be made after 5 to 14 days after the last dose. This will be done for all subjects who were treated with even one dose of the investigational product. If the withdrawal was due to AEs, the outcome for that subject will be recorded to the extent possible in the case report form (CRF) (see Section 9.1.4). If the withdrawal was due to suicidal behavior and/or suicidal ideation, appropriate measures will be implemented such as referring the subject to a specialist.

4.2.4 Stopping Rules for the Study

Refer to Section 4.2.4 of double-blind study in the protocol (DS5565-A-J303).

5. TREATMENT ADMINISTERED

5.1 Investigational Products

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

5.1.1 Study Treatments

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

5.1.1.1 Investigational Product

Investigational product code: DS-5565

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

Content and dosage form:

Name of investigational product	Content and dosage form
DS-5565 Tablets 5mg	White film-coated tablet containing 5 mg of the free form of DS-5565
DS-5565 Tablets 10 mg	White film-coated tablet containing 10 mg of the free form of DS-5565
DS-5565 Tablets 15 mg	White film-coated tablet containing 15 mg of the free form of DS-5565

5.1.2 Dosing Regimens for the Study

The duration of investigational product administration will be 52 weeks, consisting of a 2 weeks of titration and a 50 weeks of dosage adjustment period. The investigational product will be administered orally twice daily (in the morning in the same manner as double-blind study and at bedtime). The first 2 weeks will be a titration period with administration of 5 mg BID. For the second 2 weeks, the dosage will be 10 mg BID. From the fifth week, if there are no concerns in safety which the investigator judge, administration will be increased to 15 mg BID. For the following visits, the dosage may be changed to either 10 mg BID or 15 mg BID, depending on safety findings at the time of each visit.

5.1.3 Method of Assessing Treatment Compliance

All doses in this study will be self-administered orally. Each subject is to return the investigational product at every visit. Compliance will be assessed by returned tablet count. Administration of the investigational product will be recorded in the eCRF/Drug

Accountability Record (number of tablets taken, dose) at all treatment visits. If no tablets are returned, the subject will be asked whether any were discarded or thrown away, or if all of the tablets were taken orally.

5.1.4 Labeling and Packaging

DS-5565 tablets of 5 mg, 10 mg and 15 mg will be packaged separately in aluminum blister packs. The blister package of each dose will be packaged separately in a box. The box will be clearly marked "For Clinical Study Use Only," and will show the Investigational Product Code, the investigational product lot number, the name and address of the sponsor, and the expired date of the investigational product in accordance with local regulations.

5.1.5 Storage

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

5.1.6 Drug Accountability

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

5.2 Concomitant Medications and Treatments

Any concomitant medications and any concomitant treatments used by a subject during the period from his/her Visit 10 until his/her post-treatment follow-up (Visit 25), whether permitted or not, will be documented in the CRF. The route of administration, the total daily dose, the duration of use, the indication for use, and the classification of therapies will also be documented in the CRF.

5.2.1 Prohibited Concomitant Medications

The following drugs are prohibited for concomitant use from the titration period (Visit 10) through the post-treatment follow-up (Visit 25).

1) Pregabalin, gabapentin
2) Drugs that could cause irreversible retinal degeneration (phenothiazine antipsychotics, deferoxamine, quinine, quinidine, ethambutol, voriconazole, etc.)
3) Other investigational products

5.2.2 Other

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

6. STUDY PROCEDURES

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

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

6.1 Visit 10

At the beginning of the titration period, the following activities and/or examinations will be performed and 5 mg BID of new investigational product will be issued to the patient. However, if the same examinations are already performed at Visit 10 of the double-blind study, those data will be used.

- Obtain written informed consent
- Evaluate inclusion criteria and exclusion criteria
- Complete SF-MPQ
- Complete HADS
- Measure body weight
- Perform physical examination
- Perform evaluation of edema
- Perform ophthalmologic examination
- Measure blood pressure and pulse rate
- Perform 12-lead ECG
- Collect blood and urine samples for laboratory tests
- Collect blood sample for evaluation of fasting blood glucose levels
- Collect blood sample for evaluation of HbA1c
- Evaluate AEs
- Complete C-SSRS
- Perform pregnancy test (only in women of childbearing potential)
- Evaluate prior drug treatment, concomitant drugs, and concomitant therapy
- Issue the investigational product

6.2 Visit 11

After the first 2 weeks of the titration period (starting at Visit 10), the subject will come to the study site (Visit 11). At Visit 11, the following activities and/or examinations will be performed and 10 mg BID of new investigational product will be issued to the patient after the investigator or sub-investigator confirms tolerability and reviews continuation of

the treatment.

- Complete SF-MPQ
- Complete HADS
- Measure body weight
- Measure blood pressure and pulse rate
- Perform evaluation of edema
- Perform neurological examination
- Collect blood and urine samples for laboratory tests
- Evaluate AEs
- Complete C-SSRS
- Record and evaluate concomitant drugs and concomitant therapy
- Issue the investigational product
- Collect unused investigational product, and record the date of the first dose taken and review drug-taking compliance

6.3 Visit 12

Two weeks after Visit 11, the subject will come to the study site (Visit 12). The following activities and/or examinations will be performed at Visit 12. At this point, 10 mg BID or 15 mg BID of new investigational product will be issued to the patient after the investigator or sub-investigator confirms tolerability and reviews continuation of the treatment.

- Complete SF-MPQ
- Complete HADS
- Measure body weight
- Measure blood pressure and pulse rate
- Perform evaluation of edema
- Perform neurological examination
- Collect blood and urine samples for laboratory tests
- Collect blood sample for evaluation of fasting blood glucose levels
- Collect blood sample for evaluation of HbA1c
- Evaluate AEs
- Complete C-SSRS
- Record and evaluate concomitant drugs and concomitant therapy
- Collect unused investigational product, and record and review drug-taking compliance

- Issue the investigational product

6.4 Visit 13 to Visit 23

After Visit 12 , the subject will come to the study site every 4 weeks (Visit 13 to Visit 23). The following activities and/or examinations will be performed at each visit, and 15 mg BID of new investigational product will be issued to the patient after the investigator or sub-investigator confirms tolerability and reviews continuation of the treatment. If there are any safety issues, 10 mg BID of new investigational product will be issued instead.

- Complete SF-MPQ
- Complete HADS
- Perform physical examination (Visit 14, 16, 18, 20, 22)
- Measure body weight
- Measure blood pressure and pulse rate
- Perform evaluation of edema
- Perform neurological examination (Visit 14, 16, 18, 20, 22)
- Perform ophthalmologic examination (Visit 14, 16, 18, 20, 22)
- Collect blood and urine samples for laboratory tests
- Collect blood sample for evaluation of HbA1c (Visit 14, 16, 18, 20, 22)
- Collect blood sample for evaluation of fasting blood glucose levels (Visit 14, 16, 18, 20, 22)
- Evaluate AEs
- Complete C-SSRS
- Record and evaluate concomitant drugs and concomitant therapy
- Collect unused investigational product, and record and review drug-taking compliance
- Issue the investigational product

6.5 End of Treatment/Early Termination (Visit 24)

The treatment period will be completed after 52 weeks of administration (Visit 24). The following activities and/or examinations will be performed at the end of treatment/early termination.

- Complete SF-MPQ
- Complete HADS
- Perform physical examination

- Measure body weight
- Measure blood pressure and pulse rate
- Perform 12-lead ECG
- Perform evaluation of edema
- Perform neurological examination
- Perform ophthalmologic examination
- Collect blood and urine samples for laboratory tests
- Collect blood sample for evaluation of HbA1c
- Collect blood sample for evaluation of fasting blood glucose levels
- Perform pregnancy test (only in women of childbearing potential)
- Evaluate AEs
- Complete C-SSRS
- Record and evaluate concomitant drugs and concomitant therapy
- Collect unused investigational product, record the date of the last dose taken and review drug-taking compliance

6.6 Post-treatment Follow-up (Visit 25, 7 days after the completion of administration)

Follow-up observations will be conducted 7 days after the completion of administration (Visit 25). The following activities and/or examinations will be performed at follow-up.

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

7. EFFICACY ASSESSMENTS

SF-MPQ[18]

Subjects will provide a self-assessment using the SF-MPQ from Visit 10 to Visit 24.

The SF-MPQ consists of 3 parts.

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

8. PHARMACOKINETIC AND BIOMARKER ASSESSMENTS

8.1 Pharmacokinetic Variable(s)

No pharmacokinetic assessment will be performed.

8.2 Biomarker Variable(s)

No biomarker assessment will be performed.

9. SAFETY ASSESSMENTS

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

9.1 Adverse Events

9.1.1 Definition of Adverse Event

An AE is any unfavorable and unintended sign (including an abnormal laboratory value or abnormal vital sign), symptom, or disease that develops from Visit 10 to 7 days after the last dose of study medication (Visit 25), regardless of relationship to the investigational product.

Any symptom that the investigator or sub-investigator considers associated with DPN will be evaluated as an efficacy variable and will not be regarded as an AE. However, if the symptom is considered potentially related to the investigational product, such a symptom will be regarded as an AE. If any pre-existing symptom or disease is aggravated during the study period, the aggravation will be reported as an AE, and the date of confirming the aggravation will be considered the date of event onset.

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

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

- Increase in ALT or AST $\geq$ 5 x 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 T-Bil $\geq$ 2 x ULN
- ALT or AST $\geq$ 3 x ULN associated with a clinical presentation suggestive of liver injury (ie, including the appearance of fatigue, nausea, vomiting, jaundice, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia)
- Serious hepatobiliary adverse event

- Severe hepatobiliary adverse event
- Hepatobiliary Adverse event leading to Discontinuation
- Any transaminase elevation associated with a clinical presentation suggestive of Liver injury
- An elevation of ALT or AST >= 3 x ULN (without clinical presentation suggestive of liver injury)
- AE related to suicide (if there are any "yes" responses to any of the questions in the C-SSRS)

9.1.2 Items to Be Investigated Concerning Adverse Events

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

Table 9-1 Items to be Investigated for Adverse Event

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

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

Items reviewed	Content of review	
Relationship to the investigational product	Classification of relationship (in accordance with the following classifications of relationship), reason for that assessment	
Classification of relationship	Related	• The AE follows a reasonable temporal sequence from investigational product administration, and cannot be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, concomitant medications). • The AE follows a reasonable temporal sequence from investigational product administration, and is a known reaction to the drug under study or its chemical group, or is predicted by known pharmacology.
	Not related	• The AE does not follow a reasonable temporal sequence from investigational product administration, or can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, concomitant medications).
Other action taken for event	None	No treatment was required.
	Medication required	Prescription and/or over-the-counter medication was required to treat the AE.
	Hospitalization or prolongation of hospitalization required	Hospitalization was required or prolonged due to the AE, whether or not medication was required.
	Other	

9.1.3 Definition of Adverse Drug Reaction

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

9.1.4 Actions to Be Taken When Adverse Events Occur

When an AE occurs, the investigator or sub-investigator will provide appropriate treatment, will report the AE to the sponsor if necessary, and to the extent possible will monitor progress until the subject recovers or the AE is resolved or relieved. If it appears unlikely from a medical perspective that the subject will recover, this will be explained to the subject, and monitoring of the subject as a part of the clinical trial will be concluded (although the treatment for the AE will be continued). In addition, clinical trial follow-up will be terminated and the clinical trial will be concluded if the investigator or sub-investigator decides further follow-up is unnecessary for the AE

because there is no relationship between the AE and the investigational product, or if the subject refuses further follow-up.

9.2 Actions to Be Taken When Serious Adverse Events Occur

If a serious adverse event (SAE) occurs after obtaining the subject's written ICF and up to Visit 25, the investigator or sub-investigator will provide appropriate treatment for the subject and will report the event via the eCRF to the sponsor within 24 hours after becoming aware of the event. The investigator will promptly entry a detailed information of the event to the sponsor in the eCRF. SAE reports will be prepared and submitted to the head of the study site or to the Institutional Review Board (IRB), using the form and procedures specified by the study site. Detailed information regarding the procedures for reporting SAEs is provided separately, in the standard operating procedures for SAEs.

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

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

The following types of events should be reported to the sponsor as promptly as possible after becoming aware of the event via the eCRF.

- Severe hepatobiliary adverse event
- Hepatobiliary Adverse event leading to Discontinuation
- Any transaminase elevation associated with a clinical presentation suggestive of Liver injury
- An elevation of ALT or AST >= 3 x ULN (without clinical presentation suggestive of liver injury)

9.3 Exposure In Utero During Clinical Studies

Daiichi Sankyo must be notified of any subject who becomes pregnant while receiving or at the time of discontinuing the investigational product. All pregnancies must be

followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the investigator to report any pregnancy in a subject using the Exposure In Utero (EIU) Reporting form. The investigator will contact the study monitor to obtain the EIU Reporting Form upon learning of a pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (ie, post-partum complications, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, including congenital anomaly in an aborted fetus), the investigator should follow the procedures for reporting SAEs.

9.4 Clinical Laboratory Evaluations

The study site staff will collect blood and urine specimens for routine laboratory tests at specified times. Specimens will be stored under conditions stipulated in the Sample Handling Manual until they are transported for measurement. Specimens will be transported and measured by a central laboratory. Table 9-2 summarizes the laboratory parameters to be assessed and the times of assessment.

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

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

Table 9-2 Laboratory Parameters to be Assessed, and Time of Assessment

	Parameters	Time of assessment
Hematology	WBC, RBC, hemoglobin, hematocrit, platelet count, differential leukocyte (neutrophil, eosinophil, basophil, monocyte, lymphocyte) counts, reticulocyte count	Visit 10 to Visit 25
Blood chemistry	Total protein, albumin, A/G ratio, T-Bil, AST (GOT), ALT (GPT), ALP, γ-GT (γ-GTP), LDH, BUN, creatinine, uric acid, creatine kinase, total cholesterol, triglycerides, Na, K, Cl, Ca, Mg, inorganic phosphorus, bicarbonate, CRP	
Urinalysis	Standard urinalysis, including microscopic examination Specific gravity, pH, protein, glucose, ketones, urobilinogen, occult blood, RBC, WBC, bilirubin	
HbA1c	HbA1c	Visit 10, Visit 12, Visit 14, Visit 16, Visit 18, Visit 20, Visit 22, Visit 24
Fasting blood glucose	Fasting blood glucose level	Visit 10, Visit 12, Visit 14, Visit 16, Visit 18, Visit 20, Visit 22, Visit 24
Pregnancy	Qualitative test (urine)	Visit 10, Visit 24

As described in Section 4.2.1, increases in aminotrasferases have been observed in the DS-5565 development program to date. Special monitoring of such elevations during Phase 3 is described below. The Hepatic Adjudication Committee (HAC) charter includes a process by which selected cases will be adjudicated by a liver disease specialist (Section 11.10). In cases of liver laboratory abnormalities, it is important to ensure that the nature and the extent of liver injury is identified and study subjects are monitored until the liver laboratory assessments return to normal. Subjects who have any transaminase elevation associated with a clinical presentation suggestive of liver injury (ie, including the appearance of fatigue, nausea, vomiting, jaundice, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia) or an elevation of ALT or AST ≥ 3 x ULN (without clinical presentation suggestive of liver injury) at any visit should be monitored closely, according to the following:

- Repeat liver tests of at least all four of the usual serum measures (ALT, AST, alkaline phosphatase (ALP), and total bilirubin at least 2 times weekly (the first repeat should be within 48 to 72 hours of initial abnormality) until values have decreased to < 2 x ULN, then at least every 1 or 2 weeks until resolution or return to baseline. An

additional 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.

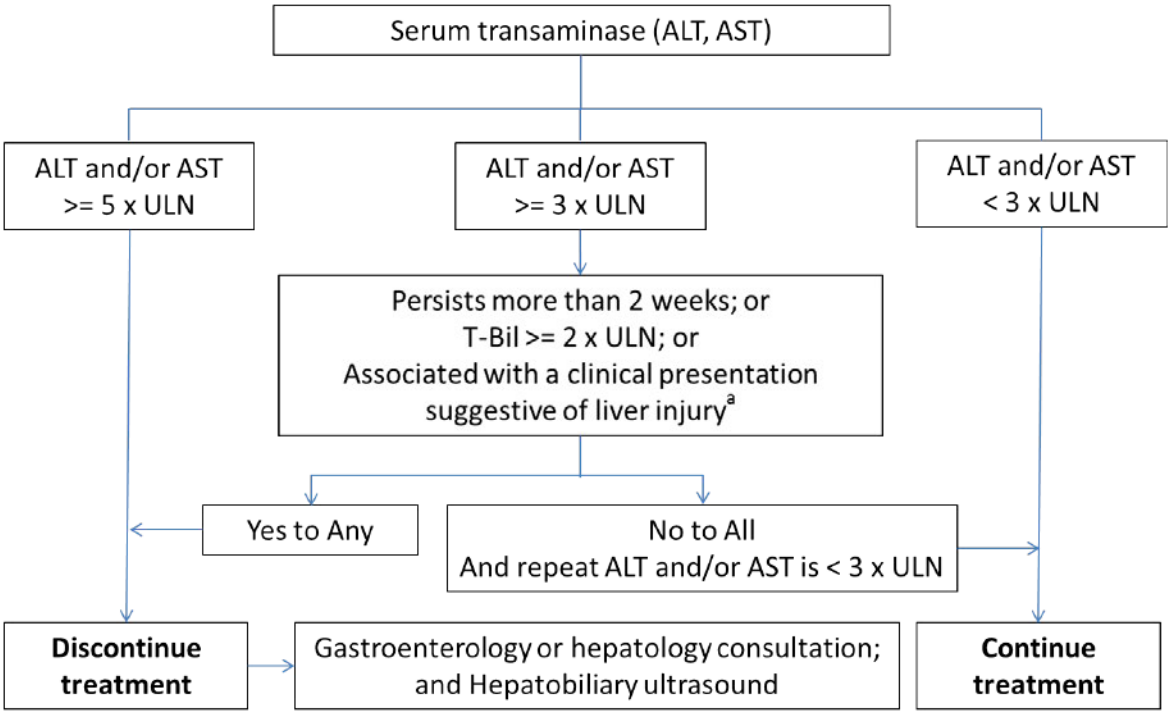
- Review or obtain a detailed history of symptoms and prior or concurrent diseases.
- Review or obtain a history of the use of concomitant drugs, including nonprescription medications, herbal and dietary supplements, alcohol, recreational drugs, and special diets.
- Rule out alcoholic hepatitis; non-alcoholic steatohepatitis (NASH); hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtain a history of exposure to environmental chemical agents.
- Perform additional liver function tests (LFTs) (eg, serum lactate dehydrogenase (LDH), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (γ-GT[γ-GTP]), prothrombin time [PT]), evaluations for potential viral etiologies (including hepatitis A, B, C, E; cytomegalovirus [CMV]; Epstein-Barr virus [EBV]) and autoimmune etiologies (anti-nuclear antibody [ANA], anti-smooth muscle antibody [ASMA], anti-mitochondrial antibody [AMA]).

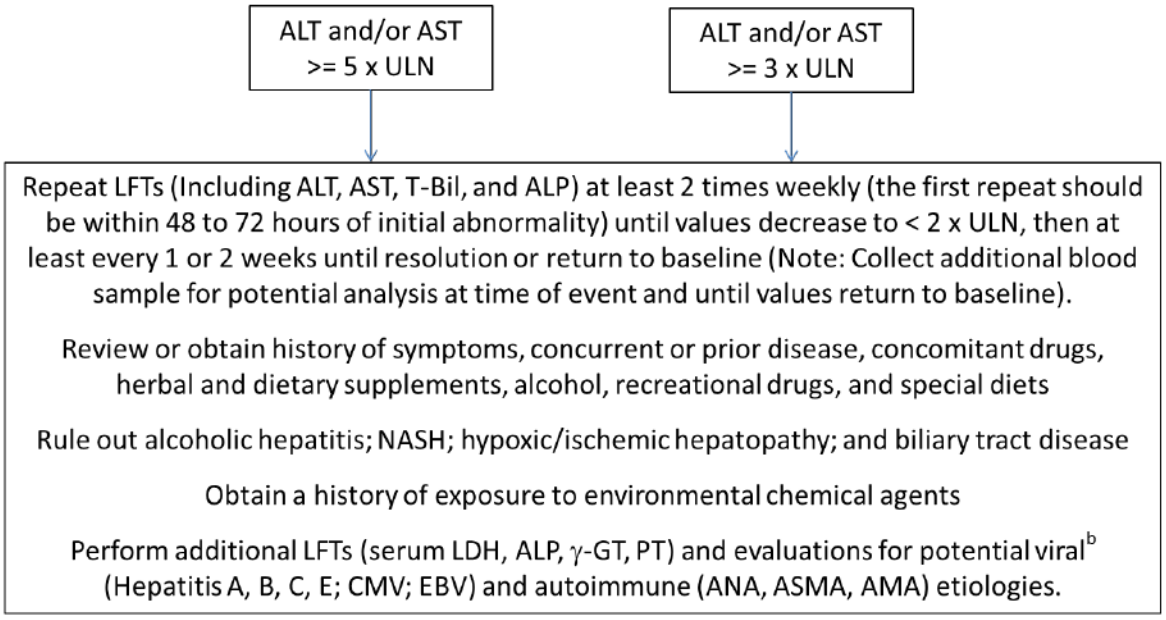
Combined elevations of aminotransferases and bilirubin meeting the criteria of a potential Hy's Law case [ALT or AST ≥ 3 x ULN with simultaneous total bilirubin ≥ 2 x ULN], either serious or non-serious and whether or not causally related, should always be reported to the sponsor within 24 hours (refer to Section 9.2), 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/Guidance/UCM174090.pdf). These events should be reported as soon as possible following the procedures outlined in Section 9.2 for SAE reporting. The sponsor will be responsible for reporting the case(s) to the FDA.

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

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

- Gastroenterology or hepatology consultation
- Hepatobiliary ultrasound





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

9.5 Vital Signs

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

9.6 Electrocardiograms

At the stipulated times (Visit 10 and Visit 24), 12-lead ECG will be performed. Results (Normal / Abnormal, not clinically significant / Abnormal, clinically significant) will be recorded in the CRF.

9.7 Physical Findings

9.7.1 Body Weight

Body weight will be measured at each visit. Results will be recorded in the CRF.

9.7.2 Physical Examinations

At Visit 10, Visit 14, Visit 16, Visit 18, Visit 20, Visit 22, Visit 24, and Visit 25 physical examination will be performed. The examination should minimally include clinical evaluations of the head, neck, thyroid, eyes, ears, nose, throat, heart, lungs, lymph nodes, abdomen, skin, extremities, and musculoskeletal system. Results will be recorded in the CRF.

9.7.3 Evaluation of Edema

Evaluation of edema will be performed, including physical examination and/or pitting, at each visit excpting Visit 25. Results (presence or absence of edema and expression site) will be recorded in the CRF.

9.8 Other Safety Assessments

9.8.1 Neurological Examination

At Visit 11, Visit 12, Visit 14, Visit 16, Visit 18, Visit 20, Visit 22, Visit 24, and Visit 25,

the abbreviated neurological examination will be performed. The assessments include muscle strength and gait/station. Each assessed results will be recorded as [Normal / Abnormal] in the CRF, based on physical examination and a medical interview.

9.8.2 Ophthalmologic Examination

The ophthalmologic examination will be performed at Visit 10, Visit 14, Visit 16, Visit 18, Visit 20, Visit 22, and Visit 24. The examination includes examination of visual acuity and funduscopic examination. For a given subject, visual acuity should be examined under the same conditions (uncorrected or corrected) at both visits, and funduscopy should be performed with the same device. Results of visual acuity will be recorded as values, and results of funduscopic examination will be recorded as [Normal / Abnormal, not clinically significant / Abnormal, clinically significant] in the CRF.

9.8.3 Columbia-Suicide Severity Rating Scale[24]

The C-SSRS is a tool designed to systematically assess and track suicidal AEs (behavior and ideation). The C-SSRS assesses lifetime suicidality during an initial baseline evaluation using standardized questions, and then prospectively monitors ideations and behaviors at subsequent follow-up assessments throughout the trial. The reviewer is an investigator or sub-investigator who has completed training prior to the study using the training DVD. The C-SSRS will be administered by the investigator or sub-investigator at each visit. Answers to all relevant questions will be recorded in the CRF. If the subject is judged to have suicidal behavior and/or suicidal ideation, appropriate measures will be implemented such as referring the subject to a specialist as described in the withdrawal procedures (see Section 4.2.3).

9.8.4 Hospital Anxiety and Depression Scale[22]

At each visit, subjects will provide a self-assessment using the HADS. The HADS consists of 7 items to score depression (4-point scale) and 7 items to score anxiety (4-point scale). The subject will respond to each item on the questionnaire. Based on the results, the investigator will check for the presence or absence of depression and/or anxiety. If the subject is judged to have an AE, appropriate measures will be implemented such as referring the subject to a specialist. Results will be recorded in the CRF.

9.8.5 Pregnancy test

Pregnancy tests (urine tests) will be conducted at the stipulated times (Visit 10 and Visit 24), for women of child-bearing potential only. All female subjects will be considered as women of child-bearing potential unless they have undergone surgical sterilization (with documented bilateral oophorectomy) or are postmenopausal and have experienced no menses within the previous 6 months. The subject is considered to be postmenopausal when 12 consecutive months of absence of menstruation is confirmed with no pathological or physiological factors. Results will be recorded in the CRF.

10. OTHER ASSESSMENTS

No other assessments will be performed.

11. STATISTICAL METHODS

11.1 Objective

To assess the long-term safety and efficacy of DS-5565 for a flexible dosing of 10 mg BID and 15 mg BID in subjects with DPNP.

11.2 General Statistical Considerations

The statistical package SAS® (Version 9.2 or higher) will be used to produce tables, figures, and listings. All safety and efficacy endpoints will be summarized for the safety analysis set.

No imputation will be done for the missing data of safety valuables. For the efficacy endpoint of SF-MPQ, a missing data will be handled using the standard scoring instructions. Details will be specified in the SAP.

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

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

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

Analysis for the change from baseline, including the shift table, will be conducted for the subjects who have an available baseline value and at least one post-enrollment (Visit 10) value.

Subgroup analyses by country (eg, Japan, Korea, and Taiwan) will be conducted for some of the efficacy and safety analyses.

A detailed SAP describing the methodology to be used in the final analysis will be prepared before the database lock. 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 Analysis Sets

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

11.4 Study Population Data

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

11.5 Efficacy Analyses

Summary statistics will be calculated for the measured value and the change from baseline in the sensory score, affective score, total score, VAS, and the present pain intensity index at each scheduled visit for the safety analysis set.

11.6 Pharmacokinetic/Biomarker Analyses

Not applicable.

11.7 Safety Analyses

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

11.7.1 Adverse Event Analyses

Any AEs that appear after the first administration of the open-label extension study, or that worsen relative to the pre-treatment state before the open-label extension study, are considered as treatment-emergent adverse events (TEAEs). TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The number and percentage of subjects reporting TEAEs will be calculated for the categories listed below. The number and percentage of subjects reporting TEAEs and ADRs will be summarized by system organ class and preferred term.

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

11.7.2 Clinical Laboratory Evaluation Analyses

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

Additionally, for ALT, AST, T-Bil, and ALP, the number and percentage of subjects who meet the criteria specified in Food Drug Administration (FDA) Drug-Induced Liver Injury (DILI) guideline[26] and evaluation of drug-induced serious hepatotoxicity (e-DISH) plot will be provided. For the urinalysis parameters excepting specific gravity, the number and percentage of subjects will be provided at each visit. Summary statistics will be tabulated for the specific gravity. A shift table will be created based on the categories of "normal" and "abnormal" between baseline and each scheduled visit.

11.7.3 Vital Sign Analyses

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

11.7.4 Electrocardiogram Analyses

A shift table will be provided for ECG evaluation between baseline and Visit 24.

11.7.5 Physical Finding Analyses

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

11.7.6 Columbia-suicide Severity Rating Scale

The data collected from C-SSRS will be tabulated.

11.7.7 Hospital Anxiety and Depression Scale

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

11.7.8 Other Safety Analyses

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

scheduled visit.

11.8 Other Analyses

Not applicable.

11.9 Data Safety Monitoring Board

Refer to Section 11.9 of double-blind study in the protocol (DS5565-A-J303).

11.10 Hepatic Adjudication Committee

Refer to Section 11.10 of double-blind study in the protocol (DS5565-A-J303).

11.11 Sample Size Determination

The long-term study is expected to enroll up to approximately 400 subjects. Of those subjects enrolled, over 150 are expected to complete 1-year treatment with DS-5565. This meets the recommendations generally agreed upon in the ICH E1 guideline (100 subjects exposed for a minimum of 1 year).

12. DATA INTEGRITY AND QUALITY ASSURANCE

Refer to Section 12 of double-blind study in the protocol (DS5565-A-J303).

12.1 Monitoring and Inspections

Refer to Section 12.1 of double-blind study in the protocol (DS5565-A-J303).

12.2 Data Collection

Refer to Section 12.2 of double-blind study in the protocol (DS5565-A-J303).
The description of ePRO is not applicable in this protocol

12.3 Data Management

Refer to Section 12.3 of double-blind study in the protocol (DS5565-A-J303).
The description of ePRO is not applicable in this protocol

12.4 Study Documentation and Storage

Refer to Section 12.4 of double-blind study in the protocol (DS5565-A-J303).
The description of ePRO is not applicable in this protocol

.

12.5 Record Keeping

Refer to Section 12.5 of double-blind study in the protocol (DS5565-A-J303).
The description of ePRO is not applicable in this protocol

13. FINANCING AND INSURANCE

13.1 Finances

Refer to Section 13.1 of double-blind study in the protocol (DS5565-A-J303).

13.2 Reimbursement, Indemnity, and Insurance

Refer to Section 13.2 of double-blind study in the protocol (DS5565-A-J303).

14. PUBLICATION POLICY

Refer to Section 14 of double-blind study in the protocol (DS5565-A-J303).

15. STUDY ADMINISTRATIVE INFORMATION

15.1 Compliance Statement, Ethics, and Regulatory Compliance

Refer to Section 15.1 of double-blind study in the protocol (DS5565-A-J303).

15.2 Subject Confidentiality

Refer to Section 15.2 of double-blind study in the protocol (DS5565-A-J303).

15.3 Informed Consent Procedures

Refer to Section 15.3 of double-blind study in the protocol (DS5565-A-J303).

15.4 Regulatory Compliance

Refer to Section 15.4 of double-blind study in the protocol (DS5565-A-J303).

15.5 Protocol Deviations

Refer to Section 15.5 of double-blind study in the protocol (DS5565-A-J303).

15.6 Supply of New Information Affecting the Conduct of the Study

Refer to Section 15.6 of double-blind study in the protocol (DS5565-A-J303).

15.7 Duration of the Study

Refer to Section 15.7 of double-blind study in the protocol (DS5565-A-J303).

15.8 Protocol Amendments

Refer to Section 15.8 of double-blind study in the protocol (DS5565-A-J303).

15.9 Study Discontinuation or Suspension

Refer to Section 15.9 of double-blind study in the protocol (DS5565-A-J303).

15.10 Organization

Refer to Section 15.10 of double-blind study in the protocol (DS5565-A-J303).

16. REFERENCES

Refer to Section 16 of double-blind study in the protocol (DS5565-A-J303).

17. APPENDICES

17.1 Schedule of Events

Table 17-1 Study Visits

	Titration period	Dosage adjustment period			End of Treatment/Early Termination	Post-treatment follow-up
Visit	**10**	**11**	**12**	**13 to 23**	**24**	**25**
Week	**14**	**16**	**18**	**Every 4 weeks**	**66**	**67**
Day	**99**	**113**	**127**	**155 to 435**	**463**	**470**
Visit window (days)		**+/-3**	**+/-3**	+/-7	+/-7	**Day 5 to 14 post-last dose**
Inclusion/exclusion criteria	X					
Body weight	X[a)]	X	X	X	X	X
Informed consent	X					
Physical examination	X[a)]			X[b)]	X	X
Evaluation of edema	X[a)]	X	X	X	X	
Neurological examination		X	X	X[b)]	X	X
Ophthalmologic examination	X[a)]			X[b)]	X	
Vital signs	X[a)]	X	X	X	X	X
12-lead ECG	X[a)]				X	
Clinical safety laboratory tests	X[a)]	X	X	X	X	X
HbA1c	X[a)]		X	X[b)]	X	
Fasting blood glucose	X[a)]		X	X[b)]	X	
C-SSRS	X[a)]	X	X	X	X	X
HADS	X[a)]	X	X	X	X	X
SF-MPQ	X[a)]	X	X	X	X	
Pregnancy test	X[a)]				X	
AE reporting	←					→
Prior and concomitant medication	X[a)]	X	X	X	X	X
Investigational product dispensing	X	X	X	X		
Investigational product compliance		X	X	X	X	

a) The result at Visit 10 in the double-blind study will be applied.
b) These will be performed on Visit 14, Visit 16, Visit 18, Visit 20, and Visit22.

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

a: After informed consent is obtained, subjects who are under treatment with the prohibited concomitant medications (see 5.2.1) will undergo a washout period of 7 days or more.
b: Body weight only.
c: These will be performed between Visit 1 and Visit 2.
d: Follow-up observation is not required for subjects who are enrolled in open-label extension study.

Table 17-2 Efficacy Assessment by Visit

	Screening	Randomization	Treatment period							End of Treatment	Post-treatment follow-up	Early Termination
Visit	1	2	3	4	5	6	7	8	9	10	11	
Week	−1	0	1	2	4	6	8	10	12	14	15	
Day	≤ −7	1	8	15	29	43	57	71	85	99	Day 7 post-last-dose	
Visit window (days)	−7 to −14	—	6 to 10	13 to 17	26 to 32	40 to 46	54 to 60	68 to 74	82 to 88	96 to 102	Day 5 to 14 post-last-dose	
Pain diaries	←	—	—	—	—	—	—	—	—	→		
Sleep interference diaries	←	—	—	—	—	—	—	—	—	→		
SF-MPQ	X	X	X	X	X	X	X	X	X	X		X
Modified BPI-SF		X								X		X
PGIC										X		X
MOS sleep scale		X								X		X
HADS		X								X		X
SF-36		X								X		X
Evaluation of Symptoms										X		X

17.2 Processing of Blood Samples for Pharmacokinetic Analyses

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

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

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