STATISTICAL ANALYSIS PLAN (SAP)

AMELA STUDY

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

-FOR DOUBLE-BLIND PHASE-

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABBREVIATION	DEFINITION
ADL	activities of daily living
ADPS	average daily pain score
ADR	adverse drug reaction
ADSIS	average daily sleep-interference score
AE	adverse event
AESI	adverse event of special interest
A/G ratio	albumin/globulin ratio
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AOR	any other reasons
ASIA	American Spinal Injury Association
AST	aspartate aminotransferase
BID	twice daily
BMI	body mass index
BOCF	baseline observation carried forward
BUN	blood urea nitrogen
Ca	calcium
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
Cl	chloride
CLcr	creatinine clearance
CNeP	central neuropathic pain
CNePSCI	central neuropathic pain after spinal cord injury
CRF	case report form
CRP	C-reactive protein
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DPNP	diabetic peripheral neuropathic pain
ECG	electrocardiogram

ABBREVIATION	DEFINITION
EQ-5D-5L	five level EQ-5D version
EQ VAS	EQ visual Analogue Scale
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GOT	glutamic oxaloacetic transaminase
GPT	glutamic pyruvic transaminase
γ-GT (γ-GTP)	gamma-glutamyl transpeptidase
HADS	hospital anxiety and depression scale
ICF	informed consent form
ICH	International Council for Harmonisation
IRT	Interactive Response Technology
ISD	intended study day
ISFLB	independent sub-functional lead of biostatistics
LDH	lactate dehydrogenase
LOCF	last observation carried forward
LOE	lack of efficacy
LS	least squares
MAR	missing at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
Mg	magnesium
MI	multiple imputation
mITT	modified intent-to-treat
MMRM	mixed effects model for repeated measurements
MNAR	missing not at random
MOS	medical outcomes study
Na	sodium
NeP	Neuropathic pain
NPSI	Neuropathic Pain Symptom Inventory
NRS	Numerical Rating Scale
OAB-SS	Overactive Bladder Symptom Score
OTC	over the counter

ABBREVIATION	DEFINITION
P	phosphate
PD	protocol deviation
PGIC	Patient Global Impression of Change
PHN	post-herpetic neuralgia
PMM	pattern mixture model
PNeP	peripheral neuropathic pain
PPS	per-protocol set
PT	preferred term
QOL	quality of life
RBC	red blood cell
REGPMM	Regression with Predictive Mean Matching
RSD	residual standard deviation
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SCI	spinal cord injury
SCIM	Spinal Cord Independence Measure
SD	standard deviation
SE	standard error
SF-MPQ	Short-Form McGill Pain Questionnaire
SOC	system organ class
T-Bil	total bilirubin
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VAS	visual analog scale
WBC	white blood cell
WHODD	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) provides a detailed, technical elaboration of the statistical analyses of efficacy and safety data as described in the study protocol Version 2.2 dated 30 Sep 2020 for DS5565-A-J314 double-blind phase. Specifications for tables, listings, and figures are contained in a separate document.

2. STUDY OBJECTIVES AND HYPOTHESIS

2.1. Objectives

2.1.1. Primary Objectives

To compare change from baseline in the weekly average daily pain score (ADPS) at Week 14 in patients with central neuropathic pain after spinal cord injury (CNePSCI) receiving mirogabalin versus placebo.

2.1.2. Secondary Objectives

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

2.1.3. Exploratory Objectives

- To evaluate the effect of mirogabalin on overactive bladder

2.2. Study Hypothesis

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

3. STUDY DESIGN AND METHODS

3.1. General Study Design and Plan

3.1.1. Study Type

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

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

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

3.1.2. Study Scheme

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

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

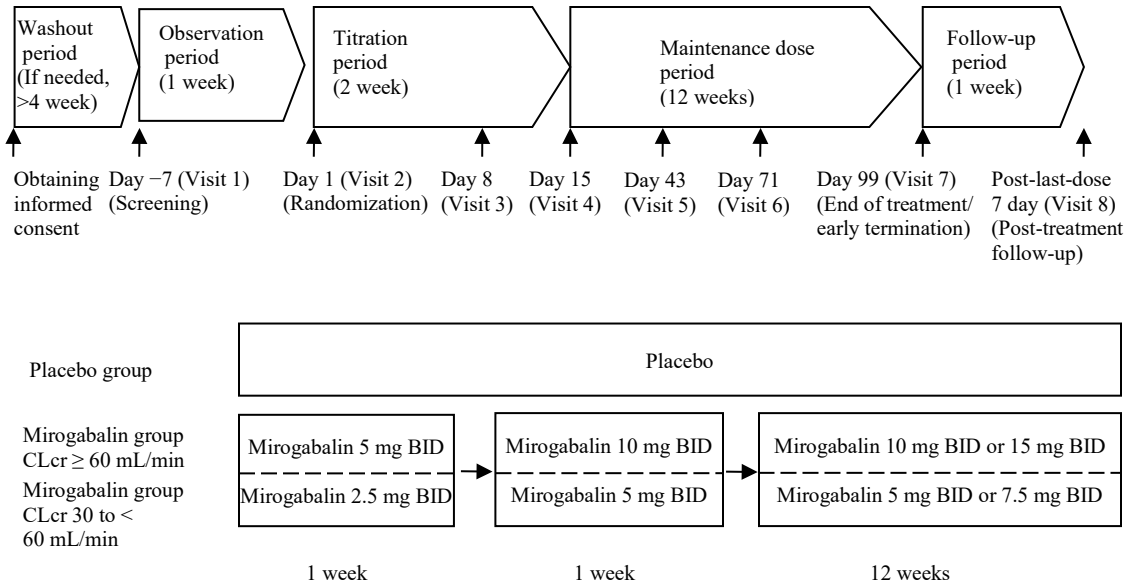
Written informed consent should be obtained before starting any examination and observations to be performed at Screening (Visit 1). After informed consent is obtained, patients who are under treatment with mirogabalin, pregabalin, or gabapentin will undergo a washout period of 28 days or more (see Section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

In mirogabalin group, patients with creatinine clearance (CLcr) ≥ 60 mL/min at Screening (Visit 1) will start with 5 mg BID of mirogabalin at first week, followed by 10 mg BID at second week as titration phase. From the third week, if there are no problems in safety, the patients will escalate the dose to 15 mg BID. For the following visits, the dosage may be changed to either 10 mg BID or 15 mg BID depending on safety findings at the time of each visit. Patients in placebo group take matching placebo throughout the entire period.

In mirogabalin group, patients with CLcr 30 to < 60 mL/min at Screening (Visit 1), will start 2.5 mg BID of mirogabalin at first week, followed by 5 mg BID at second week as titration phase. From the third week, if there are no problems in safety, the patients will escalate the dose to 7.5 mg BID. For the following visits, the dosage may be changed to either 5 mg BID or 7.5 mg BID depending on safety findings at the time of each visit. Patients in placebo group take matching placebo throughout the entire period.

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

Further details of the study procedures are provided in the Schedule of Events (See Section 3.4) and Study Procedures (See Section 6 of protocol).



3.2. Randomization

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

3.3. Blinding

The study will be a double-blind study, using matching placebo. Blinding will be applied to all personnel related to the study (subjects, investigators, sub-investigators, sponsor, and contact research organization), with the exception of the independent biostatistician, the independent sub-functional lead of biostatistics (ISFLB), and other staff involved in the preparation, release and shipment of investigational product.
Randomization schedule will be generated by the independent biostatistician and approved by the ISFLB. The independent biostatistician will share the randomization schedule with personnel specified in the randomization schedule request form. Until the study is unblinded, the randomization schedule will be kept securely.

3.4. Schedule of Events

Table 3-1 Study Visit

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

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

Table 3-2 Efficacy Assessment by Visit

	Screening	Randomization	Treatment period				End of Treatment	Post-treatment follow-up [a]	Early Termination
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Week	**−1**	**0**	**1**	**2**	**6**	**10**	**14**	**15**	
Day	**≤ −7**	**1**	**8**	**15**	**43**	**71**	**99**	**Day 7 post-last-dose**	
Visit window (days)	**−7 to −14**	**-**	**6 to 10**	**13 to 17**	**40 to 46**	**68 to 74**	**96 to 102**	**Day 5 to 14 post-last-dose**	
Pain diaries	←	—	—	—	—	—	→		
Sleep interference diaries	←	—	—	—	—	—	→		
SF-MPQ	X	X	X	X	X	X	X		X
Medical Outcome Study sleep scale		X					X		X
PGIC							X		X
NPSI		X					X		X
EQ-5D-5L		X					X		X
HADS		X					X		X
SCIM		X					X		X
Evaluation of allodynia		X					X		X
Bladder diaries[a]	←	→				←	→		
OAB-SS[a]	X						X		X

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

4. STUDY ENDPOINTS

4.1. Efficacy Endpoints

4.1.1. Primary Efficacy Endpoint[1]

Each subject will record a pain score in the patient diary once daily from the day after Screening (Visit 1) through End of Treatment/Early Termination (Visit 7). Every morning upon awakening, prior to taking study medication, the subject will select the number that best describes his or her pain over the previous 24 hours on a scale of 0 (no pain) to 10 (worst possible pain). The weekly ADPS is defined as being weekly average of the pain scores. ADPS for each week will be calculated as long as at least 1 pain score is available for the corresponding interval shown in Table 4-1. Pain scores recorded after the next day of the last dose will not be used for the calculation of ADPS.

Table 4-1 Interval for Summarizing ADPS

Analysis Time Point	Interval of Day From Randomization*
Baseline	Available pain scores in the last 7 days on or before randomization.
Week 1	Day 2 to Day 8
Week 2	Day 9 to Day 15
Week 3	Day 16 to Day 22
Week 4	Day 23 to Day 29
Week 5	Day 30 to Day 36
Week 6	Day 37 to Day 43
Week 7	Day 44 to Day 50
Week 8	Day 51 to Day 57
Week 9	Day 58 to Day 64
Week 10	Day 65 to Day 71
Week 11	Day 72 to Day 78
Week 12	Day 79 to Day 85
Week 13	Day 86 to Day 92
Week 14	Day 93 to Day 99

*Day 1 is the day of randomization (Visit 2).

4.1.2. Secondary Efficacy Endpoints

4.1.2.1. Average Daily Pain Score Response Rate[2]

Percent change in ADPS for each subject will be calculated as:

100 * (Observed ADPS - Baseline ADPS)/Baseline ADPS

Four categorical variables for ADPS will be created using percent change as follows:

- A subject with at least a 30% reduction in ADPS from baseline (i.e., a percent change of ≤ -30%) at Week 14 is considered to be a 30% responder
- A subject with at least a 50% reduction in ADPS from baseline at Week 14 is considered to be a 50% responder
- A subject with at least a 75% reduction in ADPS from baseline at Week 14 is considered to be a 75% responder
- A subject with 100% reduction in ADPS from baseline at Week 14 (i.e., ADPS at Week 14 is zero) is considered to be a 100% responder

4.1.2.2. Short-Form McGill Pain Questionnaire[3]

At every visit from Screening (Visit 1) to End of Treatment/Early Termination (Visit 7), subjects will provide a self-assessment using the SF-MPQ. The SF-MPQ consists of 3 parts:

1. 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. Methods to obtain each summary score are shown below.
   - Sensory score:
     Sum of the score of the following descriptors (range 0 to 33).
     [1. Throbbing, 2. Shooting, 3. Stabbing, 4. Sharp, 5. Cramping, 6. Gnawing, 7. Hot-burning, 8. Aching, 9. Heavy, 10. Tender, 11. Splitting]
     If any value is missed, the mean of the non-missing values from 1 to 11 will be calculated and imputed to the missing item.
   - Affective score:
     Sum of the score of the following descriptors (range 0 to 12).
     [12. Tiring-exhausting, 13. Sickening, 14. Fearful, 15. Punishing-cruel]
     If any value is missed, the mean of the non-missing values from 12 to 15 will be calculated and imputed to the missing item.
   - Total Score:
     Sum of sensory score and affective score, range 0 to 45.
2. 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.
3. A Present Pain Intensity index that provides a score of 0 to 5 (0: No pain, 1: Mild, 2: Discomforting, 3: Distressing, 4: Horrible, 5: Excruciating) based on intensity.

4.1.2.3. Patient Global Impression of Change[1]

At End of Treatment/Early Termination (Visit 7), subjects will provide a self-assessment in comparison to Randomization (Visit 2), using the 7-point scale (1: very much improved, 2: much improved, 3: minimally improved, 4: no change, 5: minimally worse, 6: much worse, 7: very much worse) in the Patient Global Impression of Change (PGIC).

PGIC score will be categorized according to the following definitions for analysis:

- Patient's overall status is minimally improved or better (i.e. score ≤ 3)
- Patient's overall status is much improved or better (i.e. score ≤ 2)

4.1.2.4. Sleep-interference Score

The Daily Sleep-Interference Diary consists of an 11-point Numerical Rating Scale (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 patient diary once daily from the day after Screening (Visit 1) through End of Treatment/Early Termination (Visit 7). Every morning upon awakening, prior to taking study medication, the subject will select the number that best describes his or her sleep-interference experience during the past 24 hours on a scale of 0 (pain did not interfere with sleep) to 10 (pain completely interfered with sleep). The weekly average daily sleep-interference score (ADSIS) is based on the sleep-interference scores from the patient daily pain diaries.

4.1.2.5. Medical Outcomes Study Sleep Scale[4,5]

At Randomization (Visit 2) and End of Treatment/Early Termination (Visit 7), subjects will provide a self-assessment using the medical outcomes study (MOS) sleep scale. The MOS sleep scale is based on questions about sleep quality during the past 4 weeks, and consists of 3 parts:

1. The average time required to fall asleep (#1)
   [0-15 minutes = 1, 16-30 minutes = 2, 31-45 minutes = 3, 46-60 minutes = 4, More than 60 minutes = 5]
2. The average hours of sleep per night, given as number of hours per night (quantity of sleep) (#2)
3. 10 questions (#3 to 12) that are given a score of 1 (all of the time) to 5 (none of the time), based on sleep disturbance in the following areas: difficulty in falling asleep or remaining asleep, difficulty in staying awake during the day, difficulty in breathing, and snoring during sleep

Based on the 12 items above, the following scales will be calculated. These scores will be calculated by OptumInsight Life Science, Inc. based on the dataset of MOS sleep scales of #1 to #12 above (See Section 8.1.1.1 for detail).

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

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

4.1.2.6. Hospital Anxiety and Depression Scale[6]

At Randomization (Visit 2) and End of Treatment/Early Termination (Visit 7), subjects will provide a self-assessment using the HADS, which will be adopted as efficacy evaluation. The HADS consists of 7 items to score depression (4-point scale: 0 to 3) and 7 items to score anxiety (4-point scale: 0 to 3).

Two subscales, depression and anxiety, will be calculated by the summing the corresponding scores for 7 items (See Section 8.1.1.2 for detail).

4.1.2.7. Neuropathic Pain Symptom Inventory[7]

At Randomization (Visit 2) and End of Treatment/Early Termination (Visit 7), subject will provide a self-assessment using the NPSI, which reflects 4 distinct dimensions of Neuropathic pain (NeP): spontaneous pain, paroxysmal pain, evoked pain, and paresthesia/dysesthesia. Each questionnaire in the dimensions has 11-point scale from 0 (no pain) to 10 (the most intense pain imaginable) to report the mean intensity of each of these items during the last 24 hours.

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

Four sub-total scores (spontaneous pain, paroxysmal pain, evoked pain, and paresthesia/dysesthesia) will be calculated by the summing the corresponding scores for above questionnaires by dimensions.

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

4.1.2.8. Five Level EQ-5D version[8]

At Randomization (Visit 2) and End of Treatment/Early Termination (Visit 7), subjects will provide a self-assessment using the Five Level EQ-5D version (EQ-5D-5L).

The EQ-5D-5L is self-administered and consists of 2 parts, the EQ-5D-5L descriptive system and the EQ visual Analogue Scale (EQ VAS). The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross)

in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1 digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5 digit number describing the respondent's health state. The numerals 1–5 have no arithmetic properties and should not be used as a cardinal score.

If any response of the EQ-5D-5L is missing then it should be coded as '9'. Ambiguous values (e.g., 2 boxes are ticked for a single dimension) should be treated as missing values.

The EQ-5D-5L health states, defined by the EQ-5D-5L descriptive system, will be converted into a single index value using value set of respective countries[19,20,21]. The EQ-5D-5L scores from subjects in Japan and Korea sites will be converted into country-specific single index value using the tariff in each supplementary material[19,20]. Index value converted with the Japanese value set will be evaluated supplementally.

The last non-missing value before the first dose of study drug will be used as the baseline value for each item of the EQ-5D-5L.

The EQ VAS records the respondent's self-rated health on a 20 cm vertical. Missing values will be coded as '999'.

4.1.2.9. Spinal Cord Independence Measure[9]

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

Three sub-total scores (self-care, respiration and sphincter management, and mobility) will be calculated by the summing the corresponding scores by categories.

4.1.2.10. Allodynia

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

1: present

2: absent

4.1.3. Exploratory Efficacy Endpoint

4.1.3.1. Average daily micturition frequency

Japanese subjects with self-urination, and who meet the diagnostic criteria of overactive bladder in Overactive Bladder Symptom Score (OAB-SS) at Screening (Visit 1) will record the micturition frequency in the bladder diary from Screening (Visit 1) to Randomization (Visit 2), and from Visit 6 to End of Treatment (Visit 7). Note: The bladder diary data will not be collected at Early Termination (Visit 7).

Average daily micturition frequency will be calculated as follows.

- Baseline – Average of daily micturition frequency between 6 days before Randomization (Visit 2) and 1 day before Randomization (Visit 2). Only the days which has the full day data will be used (days with only daytime or bedtime data will be excluded.)
- Week 14 – Average of daily micturition frequency between 6 days before End of Treatment (Visit 7) and 1 day before End of Treatment (Visit 7). Only the days which has the full day data will be used (days with only daytime or bedtime data will be excluded.) In addition, Average of daily micturition frequency between 1 day after Visit 6 and 1 day before End of Treatment (Visit 7) will be calculated as 1 month average value.

4.1.3.2. Average daily urinary incontinence episodes

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

Average daily urinary incontinence episodes will be calculated as the same method of average daily micturition frequency described in Section 4.1.3.1.

4.1.3.3. Parameters assessed using Overactive Bladder Symptom Score[10]

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

4.2. Safety Endpoint(s)

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

4.2.1. Adverse Event

All serious adverse events (SAEs) occurring after the subject signs the informed consent form (ICF) and up to 7 days after the last dose of study medication (i.e., the follow-up period), whether observed by the Investigator or reported by the subject, will be recorded on the AE section in case report form (CRF). All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

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

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

4.2.1.1. Definition of Adverse Event

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

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

4.2.1.2. Serious Adverse Event

SAE is any untoward medical occurrence that at any dose:

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

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

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

Note:

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

4.2.1.3. Severity Assessment

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

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

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

4.2.1.4. Causality Assessment

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

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

  or

  - The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its chemical group, or is predicted by known pharmacology.
- Not Related:

The AE does not follow a reasonable sequence from study drug administration, or can be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).

4.2.1.5. Action Taken Regarding Study Drug(s)

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

4.2.1.6. Other Action Taken for Event

- None.

  - No treatment was required.
- Medication required.
  - Prescription and/or over the counter (OTC) medication was required to treat the AE.
- Hospitalization or prolongation of hospitalization required.
  - Hospitalization was required or prolonged due to the AE, whether or not medication was required.
- Other.

4.2.1.7. Adverse Event Outcome

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

4.2.1.8. Definition of Adverse Drug Reaction

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

4.2.2. Significant Adverse Events

Following AEs are defined as significant AEs. List of Medical Dictionary for Regulatory Activities (MedDRA) codes are specified in Appendix 1.

- Somnolence-related
- Dizziness-related
- Cardiovascular-related
- Oedema-related
- Drug Abuse-related

- Drug withdrawal-related
- Visual disorders-related
- Loss of consciousness-related
- Cardiac failure-related
- Weight gain-related
- Glucose intolerance-related

4.2.3. Adverse Events of Special Interest

All antiepileptic drugs carry a risk of increased suicidal behavior and ideation. Furthermore, increased hepatic transaminases have been observed in the mirogabalin development program. Therefore, the following AEs will be treated as adverse event of special interest (AESI). List of MedDRA codes are specified in Appendix 1.

- Hepatic-related
- Suicide-related

4.2.4. Clinical Laboratory Evaluations

Table 4-2 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 4-2 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, Early Termination
Blood chemistry	Total protein, albumin, A/G ratio, T-Bil, AST (GOT), ALT (GPT), ALP, γ-GT (γ-GTP), LDH, BUN, creatinine, uric acid, creatine kinase, total cholesterol, triglycerides, Na, K, Cl, Ca, Mg, inorganic phosphorus, bicarbonate, PNeP	
Urinalysis	Standard urinalysis, including microscopic examination Specific gravity, pH, protein, glucose, ketones, urobilinogen, occult blood, RBC, WBC, bilirubin	
HbA1c	HbA1c	Visit 2 and Visit 7, Early Termination
Pregnancy	Qualitative test (urine)	Visit 1 and Visit 7, Early Termination

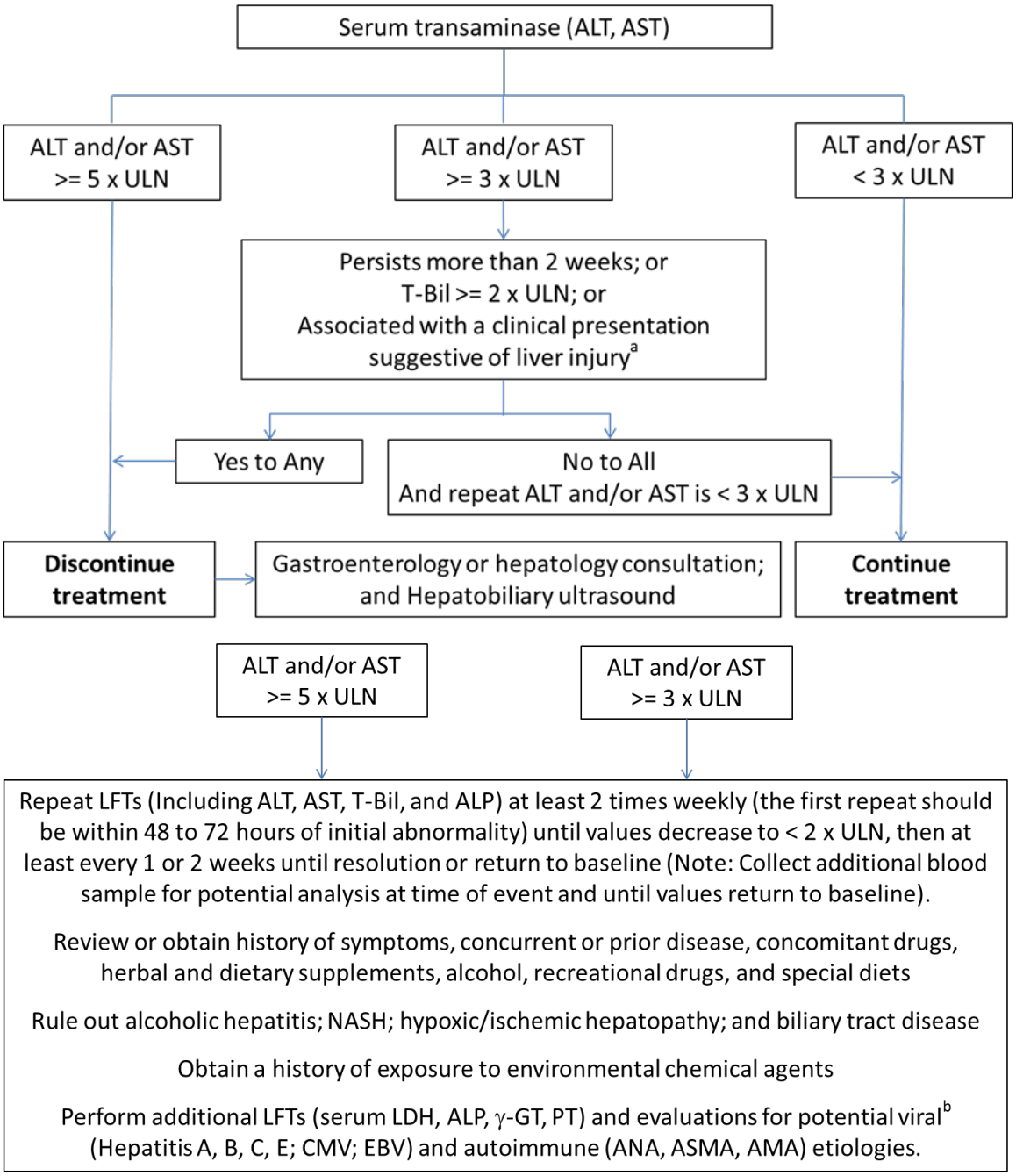
In cases of liver laboratory abnormalities, it is important to ensure that the nature and the extent of liver injury is identified and study subjects are monitored until the liver laboratory assessments return to normal. Subjects who have any transaminase elevation associated with a clinical presentation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

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

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

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

4.2.5. Vital Signs

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

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

4.2.6. Electrocardiograms

At the stipulated times (Screening [Visit 1] and End of Treatment/Early Termination [Visit 7]), 12-lead ECG will be performed. Results (Normal/Abnormal, not clinically significant/Abnormal, clinically significant) will be recorded in the CRF.

4.2.7. Physical Findings

4.2.7.1. 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.

4.2.7.2. Medical Interview

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

4.2.7.3. Evaluation of Edema

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

4.2.8. Other Examinations

4.2.8.1. Columbia-Suicide Severity Rating Scale

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

4.2.8.2. Hospital Anxiety and Depression Scale

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

4.3. Pharmacokinetic Endpoints

Not applicable.

4.4. Pharmacodynamic Endpoints

Not applicable.

4.5. Biomarkers

Not applicable.

4.6. Immunogenicity

Not applicable.

4.7. Pharmacogenomics

Not applicable.

5. SAMPLE SIZE DETERMINATION

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

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

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. Analysis Sets

6.1.1. Enrolled Subjects

Enrolled subjects will include all subjects who signed the ICF.

6.1.2. Randomized Subjects

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

6.1.3. Safety Analysis Set

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

6.1.4. Modified Intent-to-Treat Analysis Set

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

6.1.5. Per-Protocol Set

The per-protocol set (PPS) will include all randomized subjects who received at least one dose of study medication, and who were sufficiently compliant with the protocol identified by Analysis sets memorandum before the database lock. The PPS will be used for supplementary analyses.

6.2. Interim Analyses and Data Monitoring

Not applicable.

6.3. Multiple Comparisons/Multiplicity

No adjustment for multiple comparisons will be made for all analyses.

6.4. Adjustment for Covariates

Primary efficacy endpoint of weekly ADPS will be analyzed using the analysis of covariance (ANCOVA) with treatment as fixed effects and baseline ADPS as covariate to compare the change from baseline in weekly ADPS at Week 14 between mirogabalin and placebo.

For all change from baseline analyses in secondary efficacy endpoints, in general, the model will include the baseline value recorded at the randomization visit (Visit 2) or, in the case of diary data (such as ADSIS), associated with the interval immediately prior to the randomization visit (Visit 2).

6.5. Handling of discontinuations or Missing Data

Pain score will not be collected after treatment discontinuation which is intercurrent event for primary estimand of this study. Thus, missing data of pain score (actually weekly ADPS) after the treatment discontinuation needs to be imputed for the primary analysis.

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.[11,12] Reason for treatment discontinuation together with the time of the discontinuation will be used for constructing the missing data pattern in the pattern mixture model (PMM).

Missing weekly ADPS after the discontinuation will be imputed using multiple imputation (MI) method, and PMM with different shift parameters depending on the reason for discontinuation (AE, lack of efficacy [LOE], or the others) will be used in the MI to impose penalty (i.e., bad score) on the imputed weekly ADPS.

For the other efficacy endpoints, the missing data will be handled according to each section of the endpoints in Section 4.1 and Section 7.2. In addition, missing data within MOS Sleep Scale and HADS will be addressed using the standard scoring instructions for each instrument, or an appropriate method will be described in the Section 8.1.1.1 to 8.1.1.2.

Missing information of the AE including the onset date, end date, severity and relationship and the concomitant medications/therapies will be handled as specified in Section 8.2.3.

Values below the limit of quantitation for laboratory parameters will be handled as zero in the summary statistics.

No imputation will be used for the other parameters.

6.6. Multicenter Studies

No study-site factors will be included in the statistical model because the majority of the study sites are expected to enroll only a small number of subjects in the study.

6.7. Examination of Subgroups

The subgroup analyses will be performed according to the following table. The subgroup analyses such as comparison vs. placebo will not be performed if appropriate analyses cannot be performed due to small number of subjects for subgroup. For COVID-19 related subjects, the subgroup analysis will be conducted regardless of the number of subjects for each subgroup category.

Table 6-1 Subgroup Analysis

Parameter	Subgroup category	Analysis, section, analysis set
Age (years)	< 65 | ≥ 65	• Demographic and other baseline characteristics (Section 7.1.3) [safety, mITT] • Analysis for the primary efficacy endpoint (Section 7.2.1) [mITT] • Analysis for the VAS in SF-MPQ (Section 7.2.2.1.2) [mITT] • Summary of TEAEs (Sections 7.3.2.1 and 7.3.2.2) [safety]
Sex	Male | Female	
Baseline weight	< Median | ≥ Median	
Baseline CLcr (mL/min)	≥ 30 < 60 | ≥ 60 < 90 | ≥ 90	
ASIA Impairment Scale Grade	Complete (A) | Incomplete (B, C or D)	
Type of SCI	Quadriplegia | Paraplegia	
Rescue medications, prohibited concomitant medications, restricted concomitant therapies, or restricted concomitant medications	At least 1 use | No use at all	• Demographic and other baseline characteristics (Section 7.1.3) [mITT] • Analysis for the primary efficacy endpoint (Section 7.2.1) [mITT] • Analysis for the VAS in SF-MPQ (Section 7.2.2.1.2) [mITT]
	Use for 50% or more days of treatment duration (See Table 7-1) | Use for less than 50% days of treatment duration	
Washout	With washout | without Washout	
Baseline ADPS	< 6 | ≥ 6	
Causality of SCI	Turnover | Accident | Other	
Duration of SCI (months)	< Median | ≥ Median	
Duration of CNePSCI (months)	< Median | ≥ Median	
Country	Japan | Korea | Taiwan	• Subject Disposition (Section 7.1.1) • Demographic and other baseline characteristics (Section 7.1.3) [safety, mITT] • Analysis for the primary efficacy endpoint (Section 7.2.1) [mITT] • Analysis for the VAS in SF-MPQ (Section 7.2.2.1.2) [mITT] • Summary of TEAEs (Sections 7.3.2.1 and 7.3.2.2) [safety]
Subjects possibly affected by COVID-19	Yes | No	• Demographic and other baseline characteristics (Section 7.1.3) [safety, mITT] • Analysis for the primary efficacy endpoint (Section 7.2.1) [mITT]

7. STATISTICAL ANALYSIS

Estimand in this study is the mean difference mirogabalin vs. placebo for change from baseline in weekly ADPS at Week 14 in patients with moderate and over chronic central neuropathic pain (CNeP) due to traumatic spinal cord injury (SCI). The missing weekly ADPS due to study treatment discontinuation will be imputed as if the subjects continue the study up to Week 14 without any study treatment after the discontinuation.

The mITT analysis set will be used as primary efficacy analysis set for all efficacy analyses and the PPS will be used as supplementary analysis. All safety analyses will be conducted for the safety analysis set.

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.

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.

Unless otherwise specified, all analyses will be summarized by treatment arm (mirogabalin vs placebo), and percentages will be based on the number of subjects in each analysis set. Patients with at screening CLcr ≥60 mL and 30 to < 60 mL/min for dose adjustment will be merged for analysis.

The statistical terms used in this section are defined in Table 7-1.

Table 7-1 Definition of Statistical Terms

Term	Definition
Treatment arms	mirogabalin arm and placebo arm.
Modal dose	Modal dose is defined for the mirogabalin group as the dose level given for the longest duration during the treatment period. If there are more than one dose level treated for the same duration, the lower dose level will be selected. The duration of treatment to each dose level will be calculated based on the data from CRF #38, #40 and IRT information. Drug interruption (non-treated period) will not be included in any dose level. For subjects with CLcr ≥ 60 mL/min, “Low modal dose” is 5 mg BID, “Middle modal dose” is 10 mg BID, and “High modal dose” is 15 mg BID. For subjects with CLcr ≥ 30 to < 60 mL/min, “Low modal dose” is 2.5 mg BID, “Middle modal dose” is 5 mg BID, and “High modal dose” is 7.5 mg BID.
Baseline	Baseline ADPS is defined as the average of up to 7 available pain scores in the last 7 days at or before Randomization (Visit 2). Baseline ADSIS is defined as the average of up to 7 available sleep-interference scores in the last 7 days at or before Randomization (Visit 2). For other parameters, baseline value is defined as the last non-missing available value at or before Randomization (Visit 2).

Term	Definition
Age (years)	Age at informed consent will be calculated.
BMI (kg/m^2)	BMI will be calculated as follows: Weight (kg)/(Height [m])^2
CLcr (mL/min)	CLcr will be calculated as follows: • {(140 - Age) × Weight (kg)}/{72 × Serum Creatinine (mg/dL)} (for male) • 0.85 × {(140 - Age) × Weight (kg)}/{72 × Serum Creatinine (mg/dL)} (for female)
Significance level	Hypothesis tests are two-sided and performed at the 0.05 significance level.
Confidence level	Confidence level for all confidence intervals is 0.95.
Time to first TEAE (days)	Time to first TEAE is defined as follows: Onset date of first TEAE - Date of first study drug administration + 1 The derivation algorisms is the follows: Earliest Start Date among all TEAEs − Earliest Start Date among all study drug administration for DB phase For the subjects who did not experience any TEAE throughout the study, the subject will be censored as below: • Subjects who did not participate in the open-label extension study will be censored at the date of follow-up visit (Visit 8) • Subjects who participated in the open-label extension study will be censored at 14 days after the last dose of study drug or on the date of the first dose for the open-label extension study whichever comes first.
Duration of TEAE (days)	Duration of TEAE is defined as follows: Stop Date of TEAE − Start Date of TEAE + 1 If Stop Date of TEAE is missing then Date of Outcome Assessment is used.
Onset period of TEAE	Onset period is defined from start date up through stop date of TEAE. If Stop Date is missing then Date of Outcome Assessment is used.
Treatment duration (days)	Treatment duration is defined as follows: Stop date of study drug administration - Start date of study drug administration + 1
Treatment compliance (%)	Treatment compliance will be calculated as follows: Compliance (%) for mirogabalin/placebo = 100 × (total number of tablets actually taken ÷ total number of tablets to be taken)

Term	Definition
Total number of tablets to be taken	Total number of tablets to be taken is calculated as the sum tablets to be taken per each logline based on the data from CRF #38. Tablets to be taken per each logline is calculated as {(Stop Date − Start Date + 1) × 2 However, if the Stop Date and Start Date have same dates for two loglines, reduce 1 from both loglines since this suggests the dose is switched between morning and evening dose. Further, reduce 1 from the first logline since the first dose is planned from evening dose. For example: [Logline #] Start Date / Stop Date −> (Tablets to be taken per each logline) [1] 01 Jan 2019 / 11 Jan 2019 −> (20) [2] 11 Jan 2019 / 21 Jan 2019 −> (20) [3] 21 Jan 2019 / 31 Jan 2019 −> (21) [4] 01 Feb 2019 / 11 Feb 2019 −> (22) [5] 12 Feb 2019 / 22 Feb 2019 −> (22) ----------Dose interruption---------- [6] 01 Mar 2019 / 11 Mar 2019 −> (22) [7] 12 Mar 2019 / 22 Mar 2019 −> (22)
PDs due to COVID-19	Based on the CRF overall comments, protocol deviations due to COVID-19 will be categorized into the followings: • Non-compliance with visit/cycle schedule • Missed visit/cycle or assessment • Study drug interruption • Study drug reduction • Pain Score missed or affected by COVID-19 • Change of dosage of restricted concomitant medications or frequency of restricted concomitant therapies caused by COVID-19 • Other
Subjects possibly affected by COVID-19	Based on the CRF overall comments, protocol deviations due to COVID-19 will be categorized into the followings: • who did not take at least one dose of study medication due to COVID-19, • who had missing data for any endpoints including efficacy and safety due to COVID-19, • who discontinued from the study due to COVID-19, • with major or minor protocol deviations due to COVID-19, • who had AEs associated with COVID-19.

7.1. Summary of Study Data

7.1.1. Subject Disposition

The number of the following subjects will be summarized. 1 to 4 will be displayed with no percentage and 5 to 6 will be displayed with percentages based on all randomized subjects. The subgroup analyses will also be conducted according to Section 6.7.

1. Subjects who signed the informed consent
2. Subjects who were screened (Visit 1)
3. Subjects who discontinued from the study during screening (Total and by reason for discontinuation)
4. Subjects who were randomized
5. Subjects who completed the study
6. Subjects who discontinued from the study (Total and by reason for discontinuation)

The number of subjects included in each of the following analysis sets defined in Section 6.1.3 to 6.1.5 will be summarized. The reasons for exclusion from each analysis sets (specified in Section 8.1.3) will also be summarized.

7.1.2. Protocol Deviations

The number and percentage of subjects with major protocol deviations (PDs) will be summarized by the following categories for all randomized subjects. Major PDs will be listed using the following categories for all randomized subjects.

- SAE Reporting
- Informed Consent
- Eligibility Criteria (Inclusion Criteria)
- Eligibility Criteria (Exclusion Criteria)
- Investigational Product
- Concomitant Prohibited Medications
- Study Procedures

In addition, major and minor PDs which are related to COVID-19 will be listed using categories specified in Table 7-1.

7.1.3. Demographic and Baseline Characteristics

The demographic and other baseline characteristics defined in Table 7-2 will be summarized using the all randomized subjects, safety analysis set, mITT analysis set, and PPS. The subgroup analyses will also be conducted according to Section 6.7.

Table 7-2 Demographic and Other Baseline Characteristic Items

Item	Category
Age (years)	(Summary statistics will be calculated)
	< 18 years ≥ 18, < 65 years ≥ 65, < 75 years ≥ 75 years
Sex	Male | Female
Age category by sex	< 18 years, male ≥ 18, < 65 years, male ≥ 65, < 75 years, male, ≥ 75 years, male < 18 years, female ≥ 18, < 65 years, female ≥ 65, < 75 years, female ≥ 75 years, female
Country	Japan | Korea | Taiwan
Height (cm)	(Summary statistics will be calculated)
Weight (kg)	
BMI (kg/m^2)	
Baseline CLcr (mL/min)	
Baseline ADPS	
VAS (mm) in SF-MPQ at Screening (Visit 1)	
VAS (mm) in SF-MPQ at Randomization (Visit 2)	
Baseline CLcr (mL/min)	< 30 mL/min ≥ 30, < 60 mL/min ≥ 60, < 90 mL/min ≥ 90 mL/min
Baseline ADPS	< 6.0 | ≥ 6.0
Hepatobiliary history	None (No) | Present (Yes)
Psychiatric disease history	None (No) | Present (Yes)
Other significant medical/surgical history	None (No) | Present (Yes)

Item	Category
ASIA Impairment Scale Grade	A | B | C | D | E Complete (A) | Incomplete (B, C or D)
Causality of SCI	Turnover | Fall | Traffic accident | Sports accident | Other Turnover | Accident | Other
Type of SCI	Quadriplegia | Paraplegia
Site of SCI	C4, C5, C6, C7, C8, T1, T2, T3, T4, T5, T6, T7, T8, T9, T10, T11, T12
Duration of SCI (months)	(Summary statistics will be calculated)
Duration of CNePSCI (months)	
NeP region	at level | below level

7.1.4. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODD).

Any medications that were stopped at or prior to randomization (Visit 2) will be considered as prior medications. Any medications taken at any time from randomization (Visit 2) to Visit 8 (inclusive) for completers who did not participate the open-label extension study, to Visit 7 (inclusive) for completers who participated the open-label extension study, or to Visit 8 (inclusive) for subjects who discontinued the study will be considered as concomitant medications for the double-blind study. Medications taken prior to randomization (Visit 2) but with a missing stop date or with a stop date either on or after randomization (Visit 2) or marked as “continuing” will be considered concomitant instead of prior medications for the summary. In order to allocate medications to prior and concomitant categories, missing dates will be treated in a similar algorithm as missing AE dates specified in Section 8.2.3.

The number and percentages of subjects with prohibited/restricted, and prior/concomitant medications, and restricted prior/concomitant therapies will be tabulated for the safety analysis set.

7.1.5. Treatment Compliance

Number and percentage of subjects in each of the categories of treatment compliance (“≥ 80%”, “≥ 50%, < 80%”, and “< 50%”) will be summarized by treatment arm and the total of all treatment arms for randomized subjects.

7.2. Efficacy Analyses

7.2.1. Analysis for Primary Efficacy Endpoint

7.2.1.1. Primary Efficacy Analyses

The primary efficacy variable, the change from baseline in the weekly ADPS at Week 14, will be analyzed using the mITT analysis set as a primary.

Mean change from baseline in ADPS at Week 14 will be compared between mirogabalin and placebo using the following MI method and ANCOVA.

The primary imputation will be based on a “nonfuture dependence" model[11,12,13] using the pattern mixture approach with shifting parameters under the MNAR mechanism for the missing weekly ADPS data. The reason for treatment discontinuation together with the time of the discontinuation will be used to construct the missing data patterns. The statistical model used for the MI data generation will be the Markov Chain Monte Carlo (MCMC) method with adjustment for covariates of treatment group, age (<65, >=65), and sex to produce 1 monotone pattern datasets first. All levels of factor covariates should have at least 1 completed subject. Any factor levels with no completed subjects should be removed from the model. Total of 1000 imputations will be used to achieve stability of the estimates. The imputation will continue using the Regression with Predictive Mean Matching (REGPMM) method for the monotone pattern with the adjustment for covariates of age (<65, >=65) and sex using the data from placebo arm. The SAS default of k=5 closest values to the regression estimate will be considered when using REGPMM.

For the primary analysis, the subjects who discontinued study treatment before Week 14 are grouped into 3 categories: Discontinued due to AE, discontinued due to LOE, or discontinued due to any other reasons (AOR). Subjects who complete study but do not have ADPS at Week 14 will be assumed to be missing at random (MAR) (i.e., no shift will be applied).

The primary shifting parameter values corresponding to the 3 categories in the PMM will be chosen as (1.0, 1.0, 0.5) for treatment discontinuation due to AE, LOE and AOR, respectively, and the corresponding shifting amount of the weekly ADPS imputed at first missing week is given by (1.0, 1.0, 0.5)*residual standard deviation (RSD)*U(0,1) where U(0,1) is a random variable from a uniform distribution with a range of 0 to 1, and RSD is the RSD of the current week after imputation by REGPMM. RSD is calculated using a regression model with covariates of treatment group and all previous visits.

The imputed value will be set as 10 (the maximal pain score) when the imputed value of pain score is over 10 after the MCMC and Delta-Shift steps. Additionally, for treatment discontinuations 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 ANCOVA with treatment as fixed effects and baseline ADPS as a covariate.

The results of ANCOVA from each complete imputed dataset will be combined using Rubin’s rule[14], and the following statistics will be provided: least squares (LS) mean for each treatment; the corresponding standard error (SE); the LS mean for the treatment difference (vs placebo); the 2-sided 95% CI; *P* value (2-sided).

SAS programs for the MI and analyses of the primary efficacy endpoint are provided in Section 8.2.7.

In addition, applying the primary analysis above, the mean change from baseline in weekly ADPS will be compared between mirogabalin and placebo at each week.

Observed weekly ADPS together with change from baseline will be summarized weekly by treatment and week (baseline, Weeks 1 to 14, Week 14/last observation carried forward [LOCF], and Week 14/baseline observation carried forward [BOCF]) on the mITT analysis set. Besides, the imputed weekly ADPS (MI estimate) together with change from baseline will be summarized by treatment and week (baseline, Weeks 1 to 14).

The subgroup analyses will be performed according to Section 6.7. The imputed datasets generated for the primary analysis will be used for the subgroup analyses. Results of subgroup analyses will be also displayed as forest plot.

The following figures will be prepared for all subjects in mITT analysis set (i.e., will not be prepared for the subgroup analysis).

- Time course of weekly ADPS mean values and of weekly ADPS mean values ± SD (baseline, Week 1 to Week 14, Week 14/LOCF, and Week 14/BOCF) will be presented by treatment group.
- Time course of the change from baseline of weekly ADPS mean values and of weekly ADPS mean values ± SD (Week 1 to Week 14, Week 14/LOCF, and Week 14/BOCF) will be presented by treatment group.
- Time course of imputed weekly ADPS MI estimate values ± SE (for baseline, Week 1 to Week 14) and changes to baseline ± SE (for Week 1 to Week 14) will be presented by treatment group.

7.2.1.2. Sensitivity Analysis for Primary Efficacy Variables

The following sensitivity analyses will be conducted to explore the robustness of inferences from the main estimator of the primary analysis.

7.2.1.2.1. Primary MNAR Model with Different Shift Parameters

The primary analysis model described in Section 7.2.1.1 will be applied with the following different shift parameters using the mITT analysis set.

(AE, LOE, AOR) = (3, 3, 1.5), (5, 5, 2.5), and (0, 0, 0)

7.2.1.2.2. Primary MNAR Model Considering Treatment Discontinuation due to COVID-19

In the primary analysis model described in Section 7.2.1.1, the treatment discontinuation due to COVID-19 pandemic will be categorized into “any other reason (AOR)” and shift parameter (penalty) of 0.5 will be used to impute weekly ADPS data just after the treatment discontinuation. However, it would be reasonable to assume that the mechanism of missing data caused by the treatment discontinuation due to COVID-19 pandemic can be missing completely at random or MAR[15]. In addition, the primary estimand of this study should be still to estimate

the treatment difference (mirogabalin vs. placebo) under the situation where COVID-19 pandemic dese not occur. Therefore, if there is any subjects who discontinued the treatment due to COVID-19 pandemic and the analysis can be applicable, a sensitivity analysis will be performed using the primary analysis model with shift parameter of 0 for subjects who discontinued the treatment due to COVID-19 pandemic. The mITT analysis set will be used for the sensitivity analysis.

7.2.1.3. Supplementary Analysis for Primary Efficacy Variables

To provide additional insights into the understanding of the treatment effect, the following supplementary analyses will be conducted in addition to the primary and sensitivity analyses.

7.2.1.3.1. Primary MNAR Model using Per-Protocol Set

The above primary "nonfuture dependence" MNAR model will be applied with the same shift parameters as the primary analysis (i.e., (1.0, 1.0, 0.5)) using PPS.

7.2.1.3.2. Placebo Multiple Imputation

The mean change from baseline in ADPS at Week 14 will be compared between mirogabalin and placebo using the following placebo MI method[16,17] and ANCOVA on mITT analysis set.

The MCMC method will be used with adjustment for covariates to produce a monotone pattern first. The same covariates as selected in the primary analysis described in Section 7.2.1.1 (except treatment) will be used in the MCMC method. For the monotone pattern data of the subjects discontinued due to any reasons in mirogabalin and placebo arms, the REGPMM method will be used to impute the missing weekly ADPS data with the same set of covariates based on information from the placebo arm. The imputed value will be set as 10 (the maximal ADPS) when the imputed value of ADPS is over 10.

7.2.1.3.3. ANCOVA using BOCF Approach

Change from baseline in ADPS at Week 14 for mirogabalin arm will be compared with the placebo arm using ANCOVA with treatment as a fixed effect and baseline ADPS as a covariate. The analysis will provide the same statistics as the analysis described in Section 7.2.1.1. The missing ADPS data at Week 14 will be imputed using the BOCF approach, which is defined as follows: If a subject completed the study and provided pain scores for all 7 days of Week 14, then the endpoint is defined as the average of the 7 daily pain scores at Week 14. If a subject completed the study but had missing pain scores during Week 14, then the missing daily pain data is replaced with the baseline ADPS scores for that subject and the endpoint will be the average of the 7 daily pain scores at Week 14. If a subject discontinued the study treatment, then the endpoint is the baseline ADPS scores for that subject.

7.2.1.3.4. ANCOVA using LOCF Approach

Change from baseline in ADPS at Week 14 for mirogabalin arm will be compared with placebo arm using ANCOVA with treatment as a fixed effect and baseline ADPS as a covariate. The analysis will provide the same statistics as the analysis described in Section 7.2.1.1.

The missing ADPS data at Week 14 will be imputed using the LOCF approach, which is defined as the average of the last seven available pain scores obtained from the day after the

Randomization (Visit 2) (i.e., the date of randomization + 1) to the next day of the last dose. If fewer than seven pain scores are available after the Randomization (Visit 2), then the ADPS will be calculated from those that are available.

7.2.2. Secondary Efficacy Analyses

All secondary efficacy endpoints will be analyzed using the mITT analysis set (primary) and PPS (sensitivity). For all secondary endpoints, the summary statistics or frequency tables will be created by treatment and week/scheduled time point, and mirogabalin arm will be compared with placebo arm. No adjustment will be made for multiple comparisons because the secondary efficacy analyses are for exploratory purpose.

7.2.2.1. Key Secondary Efficacy Analyses

7.2.2.1.1. ADPS Responder Rate

Response rate, which is defined as the proportion of subjects with ≥ 30%, ≥ 50%, ≥ 75%, and 100% reduction from baseline in ADPS (Section 4.1.2.1) at Week 14, will be calculated. Response rates of 30%, 50%, 75%, and 100% reduction will be compared between mirogabalin and placebo using a logistic regression model with treatment as a factor and baseline ADPS as a covariate. The logistic regression model will be also used to construct the 95% CIs for odds ratio between treatment groups.

Continuous responder analysis[18], which represents the cumulative distribution of the percent reduction from baseline in ADPS, will be performed at Week 14 for graphical evaluation.

ADPS values at Week 14 will be imputed using LOCF approach for the subjects who completed the study but did not have available ADPS data at Week 14. The subjects who discontinued the study will be considered as non-responders.

```
proc logistic data=DATASET;
    class TRT01PN / param=ref;
    model AVAL (ref="0") = TRT01PN BASE;
    /* AVAL and BASE are response (0=nonresponse) and baseline ADPS, respectively */
run;
```

7.2.2.1.2. Short-Form McGill Pain Questionnaire

For the sensory score, affective score, total score, VAS, and the present pain intensity index (Section 4.1.2.2), summary statistics will be computed for the measured value and the change from baseline by scheduled time point (including Week 14/LOCF). For the VAS and change from baseline in VAS, the arithmetic mean with the corresponding SD will be plotted over time by week (including Week 14/LOCF).

The change from baseline to Week 14/LOCF in sensory score, affective score, total score, VAS, and present pain intensity will be compared between mirogabalin and placebo using the ANCOVA model with baseline value as a covariate. The same statistics will be provided as for the ADPS (Section 7.2.1.1).

The subgroup analyses will be conducted according to Section 6.7.

7.2.2.1.3. Sleep-interference Score

The summary statistics for the observed ADSIS and change from baseline in ADSIS will be provided by week (Baseline, Weeks 1 to 14, and Week 14/LOCF). The arithmetic mean with the corresponding SD will be plotted over time by week (including Week 14/LOCF) for the ADSIS and change from baseline in ADSIS.

The change from baseline in ADSIS at Week 14/LOCF for mirogabalin arm will be compared with that for placebo, using the ANCOVA model with treatments as a fixed effect and baseline ADSIS as a covariate. The same statistics as the analysis of ADPS in Section 7.2.1.1 will be provided

7.2.2.1.4. Patient Global Impression of Change

The PGIC score (Section 4.1.2.3) at Week 14 will be described in a frequency table.

The proportion of subjects who scored “minimally improved or better” (i.e. score ≤ 3) and “much improved or better” (i.e. score ≤ 2) will be compared between mirogabalin and placebo using a logistic regression model with treatment as a factor. The logistic regression model will be also used to construct the 95% CIs for odds ratio between treatment groups.

PGIC values at Week 14 will be imputed using LOCF approach for the subjects who completed the study but did not have available PGIC data at Week 14. The subjects who discontinued the study will be considered as non-responders.

7.2.2.1.5. Medical Outcomes Study Sleep Scale

For the subscales of sleep disturbance, quantity of sleep, snoring, awakening short of breath or with a headache, sleep adequacy, somnolence, and the 9-item sleep problems index (Section 4.1.2.5), the summary statistics of subscale and change from baseline in subscale will be provided by scheduled time point (including Week 14/LOCF). The change in each subscale from baseline to Week 14/LOCF will be compared between mirogabalin and placebo using the ANCOVA model with baseline value as a covariate. The same estimates as the analysis for the ADPS in Section 7.2.1.1 will be provided.

For optimal sleep, the number of subjects and their percentages will be provided by scheduled time point (including Week 14/LOCF). A logistic regression model with treatment as a factor will be used to compare the subjects who reported “Optimal sleep (Yes)” at Week 14/LOCF between mirogabalin and placebo. The logistic regression model will be also used to construct the 95% CIs for odds ratio between treatment groups.

7.2.2.1.6. Hospital Anxiety and Depression Scale

For the two subscales of Depression and Anxiety (Section 4.1.2.6), the subscale and change from baseline in subscale will be summarized by scheduled time point (including Week 14/LOCF).

The change from baseline to Week 14/LOCF will be compared between mirogabalin and placebo using the ANCOVA model with baseline value as a covariate. The same estimates as the analysis for the ADPS in Section 7.2.1.1 will be provided.

7.2.2.1.7. Neuropathic Pain Symptom Inventory

The sub-total score of each dimension (spontaneous ongoing pain, spontaneous paroxysmal pain, evoked pain, and paresthesia/dysesthesia) and total score will be summarized by scheduled time point (including Week 14/LOCF). The change from baseline at Week 14/LOCF will be compared between mirogabalin and placebo using the ANCOVA model with baseline value as a covariate. The same estimates as the analysis for the ADPS in Section 7.2.1.1 will be provided.

7.2.2.1.8. EQ-5D-5L

The index value, derived using the value set of respective countries[19,20,21], and VAS will be summarized by scheduled time points (including Week 14/LOCF). The change from baseline in the index value and VAS will be also summarized by scheduled time points (including Week 14/LOCF). The change from baseline in the index value and VAS at Week 14/LOCF and at Week 14 will compared between mirogabalin and placebo using the ANCOVA model with baseline value as a covariate. The same estimates as the analysis for the ADPS in Section 7.2.1.1 will be provided. The arithmetic mean of measured value and change from baseline with the corresponding SD will be plotted at scheduled time points (including Week 14/LOCF).

For the index value derived using Japanese value set[19] for all subjects, the same analyses as that above will be performed.

7.2.2.1.9. Spinal Cord Independence Measure

For the sub-total score of each category (self-care, respiration and sphincter management, and mobility) and the total score, the change from baseline will be compared between mirogabalin and placebo. The sub-total score of each category (self-care, respiration and sphincter management, and mobility) and total score will be summarized by scheduled time point (including Week 14/LOCF). The change from baseline at Week 14/LOCF will be compared between mirogabalin and placebo using the ANCOVA model with baseline value as a covariate. The same estimates as the analysis for the ADPS in Section 7.2.1.1 will be provided.

7.2.2.1.10. Evaluation of Allodynia

A shift table presenting the change from baseline in allodynia ([at level] and [below level] respectively) will be prepared for mirogabalin and placebo. Percentages of subjects who shifted from present to absent will be calculated for [at level] and [below level] respectively and compared between mirogabalin and placebo at Week 14/LOCF by logistic regression model with treatment as a factor. The logistic regression model will be also used to construct the 95% CIs for odds ratio between treatment groups.

7.2.3. Other Secondary Efficacy Analyses

Not Applicable.

7.2.4. Exploratory Efficacy Analysis

7.2.4.1. Evaluation of Average Daily Micturition Frequency

The summary statistics for the observed value and the change from baseline in the average daily micturition frequency to Week 14/LOCF (including 1 month average for Week 14) will be provided by scheduled time point.

7.2.4.2. Evaluation of Average Daily Urinary incontinence episodes

The summary statistics for the observed value and the change from baseline in the average daily urinary incontinence to Week 14/LOCF (including 1 month average for Week 14) will be provided by scheduled time point.

7.2.4.3. Evaluation of parameters assessed using Overactive Bladder Symptom Score

OAB-SS questions will be transformed to numeric scores according to 8.1.1.3. For respective scores and total score, summary statistics of observed scores at Screening (Visit 1) and End of Treatment/Early Termination (Visit 7) will be summarized. Also, change in total score from Screening (Visit 1) to Week 14/LOCF will be compared between mirogabalin and placebo using the ANCOVA model with baseline value as a covariate. In addition, the arithmetic mean of observed scores and change from baseline with corresponding SD will be plotted at Screening (Visit 1) and End of Treatment/Early Termination (Visit 7).

7.3. Safety Analyses

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

7.3.1. Exposure to Study Treatment and Product Characteristics

Treatment duration (days) will be summarized as summary statistics by treatment arm and the total of all treatment arms using the safety analysis set. Further, the number and percentage of subjects with treatment duration ≥ 2 weeks, ≥ 4 weeks, ≥ 6 weeks, ≥ 8 weeks, ≥ 10 weeks, ≥ 12 weeks, and ≥ 14 weeks will be provided.

In addition, the number and percentage of subjects will be also summarized by modal dose of mirogabalin (the most frequent administered dose level during the treatment period; See Table 7-1) .

7.3.2. Adverse Events

The analysis of AEs will be provided for all TEAEs. TEAE is defined as any AE that emerges on or after first dosing and during the duration of the study treatment (having been absent prior to treatment) or worsens relative to the pre-treatment state. The duration of the study treatment is considered as:

- For subjects who did not participate in the open-label extension study – Until follow-up visit (Visit 8) or 14 days after the last dose of study drug whichever is earlier.

- For subjects who participated in the open-label extension study – Until 14 days after the last dose of study drug in the double blind study or the first dose of study drug in the open-label extension study whichever is earlier.

Detailed logic of treatment-emergent is defined in Section 8.1.2.1.

All AE analysis will be performed by treatment arm and overall.

The AEs will be coded using the MedDRA Version 23.0.

7.3.2.1. Summary of Treatment-Emergent Adverse Events

The number and percentage of subjects with the following TEAEs will be summarized. The subgroup analyses will also be conducted according to Section 6.7.

- TEAE
- ADR
- Serious TEAE
- Serious ADR
- Severe TEAE
- Severe ADR
- Significant TEAE
- Significant ADR
- TEAE associated with treatment discontinuation
- ADR associated with treatment discontinuation

7.3.2.2. Treatment-Emergent Adverse Event Classified by System Organ Class and Preferred Term

The number and percentage of subjects with the following TEAEs will be summarized by system organ class (SOC) and preferred term (PT). If the same TEAE occurs multiple times in the same subject, only the most severe event will be included in the summary by severity. The SOC and PT will be displayed in Japanese as well as English. The subgroup analyses (only TEAE and TEAE by severity) will also be conducted according to Section 6.7.

- TEAE
- ADR
- TEAE by severity
- ADR by severity
- Serious TEAE
- Serious ADR
- Serious TEAE by severity

- Serious ADR by severity
- TEAE associated with treatment discontinuation
- ADR associated with treatment discontinuation

7.3.2.3. Significant Adverse Events

Number and percentage of subjects with each significant TEAE specified in section 4.2.2 will be summarized as below. If a subject experiences more than one episode of AE with the same category of the significant AEs, the subject will be counted once for that category at the maximum severity.

If there is multiple SOC or PT occurred for the same subject, most severe event will be adopted for by severity analysis.

- Significant TEAE
- Significant TEAE by severity
- Serious significant TEAE
- Significant TEAE associated with treatment discontinuation

If there are multiple AEs of the same severity, the outcome of the first AE will be used.

- Outcome of significant TEAE
- Outcome of significant TEAE associated with treatment discontinuation

Further, time to first onset (in days) and duration (in days) of significant TEAEs will be summarized as median, minimum, and maximum values.

- Significant TEAE by time to first onset (in days)
- Significant TEAE by duration (in days)

In addition, additional analyses for selected significant TEAEs will be performed according to section 7.3.2.3.1 and 7.3.2.3.2.

7.3.2.3.1. Somnolence/Dizziness with Fall and Injuries

Out of the subjects who experienced somnolence-related or dizziness-related TEAEs, the number and percentage of subjects who had fall and injuries-related TEAEs (details specified in Appendix 1) during the onset period of somnolence-related or dizziness-related TEAEs will be calculated.

7.3.2.3.2. Oedema with cardiovascular / respiratory

Out of the subjects who experienced oedema-related TEAEs, the numbers and percentages of subjects who had cardiovascular-related TEAEs and subjects who had respiratory related-TEAEs (details specified in Appendix 1) will be calculated, respectively.

7.3.2.4. Adverse Events of Special Interest

The same analysis as section 7.3.2.3 will be performed for each TEAEs of special interest specified in section 4.2.3.

7.3.2.5. Time to First Treatment-Emergent Adverse Event

Kaplan-Meier product limit method will be used to provide Kaplan-Meier curve of time to first onset of any TEAEs, any ADRs and each significant TEAEs/ADRs specified in section 4.2.2.

7.3.3. Death, Other Serious Adverse Events

Deaths, SAEs, and TEAE associated with treatment discontinuation will be listed.

7.3.4. Clinical Laboratory Evaluations

For the hematology, blood chemistry parameters and HbA1c, summary statistics of measured value and change from baseline will be summarized at each scheduled time point. Also, a shift table (abnormal low/normal/abnormal high) between baseline and each scheduled time point will be provided. The arithmetic mean of measured value and change from baseline with corresponding SD will be plotted at scheduled time points.

For the urinalysis parameters except for specific gravity, the number and percentage of subjects for each measured category will be provided at each scheduled time point. For specific gravity, summary statistics will be tabulated in the same way as for hematology and blood chemistry parameters. A shift table (normal/abnormal [or abnormal low/normal/abnormal high if applicable]) between baseline and each scheduled time point will be created.

Additionally, for ALT, Aspartate Aminotransferase (AST), T-Bil, and ALP between the first dose of study treatment and the follow-up period (Visit 8), the number and percentage of subjects whose values meet the criteria specified in food and drug administration (FDA) drug-induced liver injury (DILI) guideline[22] (See Table 7-3 for detail) will be summarized.

Table 7-3 Criteria of FDA DILI Guideline

Parameter	Category
ALT	≥ 3 x ULN, ≥ 5 x ULN, ≥ 8 x ULN, ≥ 10 x ULN, ≥ 20 x ULN
AST	≥ 3 x ULN, ≥ 5 x ULN, ≥ 8 x ULN, ≥ 10 x ULN, ≥ 20 x ULN
ALT, AST	ALT and/or AST ≥ 3 x ULN, ≥ 5 x ULN, ≥ 8 x ULN, ≥ 10 x ULN, ≥ 20 x ULN
T-Bil	≥ 1.5 x ULN, ≥ 2 x ULN
ALP	≥ 1.5 x ULN
ALT and T-Bil	ALT ≥ 3 x ULN and T-Bil ≥ 2 x ULN (at the same visit), ALT ≥ 3 x ULN and T-Bil ≥ 2 x ULN (within an arbitrary 30-day periods)
AST and T-Bil	AST ≥ 3 x ULN and T-Bil ≥ 2 x ULN (at the same visit), AST ≥ 3 x ULN and T-Bil ≥ 2 x ULN (within an arbitrary 30-day periods)

Parameter	Category
(ALT and/or AST), ALP and T-Bil	(ALT ≥ 3 x ULN and/or AST ≥ 3 x ULN), ALP < 2 x ULN, and T-Bil ≥ 2 x ULN (at the same visit)
	(ALT ≥ 3 x ULN and/or AST ≥ 3 x ULN), ALP < 2 x ULN, and T-Bil ≥ 2 x ULN (within an arbitrary 30-day periods)

In addition, an evaluation of drug-induced serious hepatotoxicity (e-DISH) plot of peak T-Bil vs peak ALT, and peak T-Bil vs peak AST will be created. The peak value will be computed in the values from the first dose to the completed/discontinued date which is Visit 7 for the completers and date of withdrawal/discontinuation for withdrawal, respectively. The graph will display a single point for each subject. The scales will be multiples of ULN. Vertical lines at 3 times the ULN will be drawn from the x-axis (ALT/AST), and a horizontal line will be drawn at 2 times the ULN from the y-axis (T-Bil).

7.3.5. Vital Signs

For systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate, summary statistics of measured values and changes from baseline will be summarized by each scheduled time point. The arithmetic mean of the measured value with the corresponding SD will be plotted for each scheduled time point.

7.3.6. Electrocardiogram

A shift table will be provided for ECG evaluation between baseline and End of Treatment/Early Termination (Visit 7).

7.3.7. Physical Findings

7.3.7.1. Body Weight

For the measured value of body weight and change from baseline, summary statistics will be calculated by each scheduled time point. The arithmetic mean of measured value and change from baseline in body weight with the corresponding SD will be plotted for each scheduled time point. Also, a scatter plot will be created for the measured value of body weight between baseline and End of Treatment/Early Termination (Visit 7).

Percent change in weight will be categorized by ≤−10%, −10< − ≤−5%, −5< − ≤0%, 0< − <5%, 5≤ − <10% and 10%≤ per each timepoint.

7.3.7.2. Evaluation of Edema

The results (presence or absence) of edema evaluation will be displayed in shift tables between baseline and End of Treatment/Early Termination (Visit 7) for each expression site.

7.3.8. Other Examinations

7.3.8.1. Columbia-Suicide Severity Rating Scale

The number and percentages of subjects with positive results of C-SSRS and with negative results of C-SSRS will be summarized. A positive result is defined as at least 1 answer of "Yes" in the entire questionnaire. A negative result is one in which all answers are "No".

7.3.8.2. Hospital Anxiety and Depression Scale

For the 2 subscales of Depression and Anxiety (Section 4.2.8.2), the subscale and change from baseline in subscale will be summarized by scheduled time point.

7.4. Pharmacokinetic and Pharmacodynamic Analyses

Not applicable.

7.5. Biomarkers Analysis

Not applicable.

8. STUDY ENDPOINT DERIVATION DETAILS, DATA HANDLING, AND REPORTING CONVENTIONS

8.1. Study Endpoints Derivation Details

8.1.1. Efficacy Endpoints Derivation Details

8.1.1.1. Calculation of MOS Sleep Scale-Revised

MOS Sleep Scale-Revised (MOS Sleep-R) will be calculated by OptumInsight Life Science, Inc. according to the following algorithm and provided with Daiichi-Sankyo.

Scoring:

There are 5 steps involved in scoring the MOS Sleep–R:

1. Step 1: Data Cleaning

Raw responses for each item must be checked for the proper range. All items in the MOS Sleep–R have 5 response categories, except item #2. Item 2 asks the individual to report on average the number of hours slept each night during the past 4 (or 1) weeks, which has a possible range of 0-24. Out of range responses should be set to missing.

2. Step 2: Item Recoding

Sleep items 1 (SLEEP1), 4 (SLEEP4) and 12 (SLEEP12) must be reverse scored so that a higher response value is indicative of better sleep.

3. Step 3: Calculating Raw Scale Scores

After item recoding (see step 2), a total raw score is computed for each sleep scale. The total raw score is a simple algebraic mean of the of the final response values for all items in a given scale, as shown in Table 8-1 below.

Table 8-1 Assignment of Sleep Items to Scales and Values Used in Calculating Raw Scale Scores

Scale	Mean of Final Response Values (after recoding, see Step 2)	Lowest and highest total raw scores	Total raw score range
Sleep Disturbance	(Sleep1_r + Sleep3 + Sleep7 + Sleep8)/4	1, 5	4
Snoring	Sleep10	1, 5	4
Shortness of Breath	Sleep5	1, 5	4
Sleep Adequacy	(Sleep4_r + Sleep12_r)/2	1, 5	4
Sleep Somnolence	(Sleep6 + Sleep9 + Sleep11)/3	1, 5	4
Sleep Problems Index 1	(Sleep4_r + Sleep5 + Sleep7 + Sleep8 + Sleep9 + Sleep12_r)/6	1, 5	4

Scale	Mean of Final Response Values (after recoding, see Step 2)	Lowest and highest total raw scores	Total raw score range
Sleep Problems Index 2	(Sleep1_r + Sleep3 + Sleep4_r + Sleep5 + Sleep6 + Sleep7 + Sleep8 + Sleep9 + Sleep12_r)/9	1, 5	4

The Optimal Sleep Scale is calculated as a 0 or a 1 scale. Item SLEEP2 is used to calculate the scale. If SLEEP2 is missing, the scale is missing. If SLEEP2 >= 7 and SLEEP2 <= 9 then SLEEP_OP1 = 1 otherwise SLEEP_OP1 = 0.

The Sleep Quantity Scale is simply the number of hours reported on item SLEEP2. There is no recoding or transformation of the number of hours of sleep reported for this scale. The Full Missing Score Estimation method, which is a standard method in OptumInsight Life Science, Inc., applies for computing scores when item response values are missing.

4. Step 4: Transformation of Raw Scale Scores to 0-100 Scale Scores

The next step in scoring consists of transforming each total raw scale score to a 0-100 scale score using the following formula:

Transformed Scale Score =

(Raw Scale Score – Lowest Raw Score) / Raw Score Range * 100

where Raw Scale Score is the raw mean score computed in Step 3 for each scale. The Lowest Raw Score is a value of 1 for each scale and the Raw Score Range is 4 for each scale. For example, a Raw Score of 3 for the Sleep Disturbance scale would be transformed as follows:

(3 – 1) / 4 * 100 = 50

where the lowest possible Sleep Disturbance raw scale score equals 1 and the possible range of Sleep Disturbance raw scale score equals 4. This transformation converts the lowest and highest possible raw scores to 0 and 100, respectively. Scores between these values represent the percentage of the total possible score achieved.

5. Step 5. T-Score Transformation (Norm-Based Scores) of 4-Week Recall MOS Sleep–R (Standard Recall Form)

This step involves the norm-based scoring of each 0-100 scale score computed in Step 4. Norms necessary to complete this step are available from QualityMetric Incorporated. The means and SDs used in the scoring step come from the 2009 general U.S. population and are used in the norm-based scoring of the scales and summary indexes of the MOS Sleep–R. A linear T-score transformation is used so that all scales and indexes have a mean of 0 and SD of 1 in the 2009 general U.S. population.

The first step in norm-based scoring consists of standardizing each scale and summary index of the MOS Sleep–R using a T-score transformation. A T-score for each scale is computed by subtracting the 2009 general U.S. population mean for each sleep scale from the 0-100 score for that scale, then dividing the difference by the corresponding sleep scale SD in the general U.S. population.

The final step involves transforming each T-score computed in the step above to a norm-based score using the formulas below. This is accomplished by multiplying each T-score (calculated using the instructions above) by 10 and adding 50 to the resulting product.

8.1.1.2. Calculation of Hospital Anxiety and Depression Scale

Listed below are the questions on the HADS and the response for each. The relation column indicates what subscale the question should be mapped to. The scoring for each subscale, Anxiety and Depression is calculated by taking the sum of each of the subscales. Two subscales of Anxiety and Depression will be created by summing the seven corresponding scores (0 to 3) below. If one or more of the seven questions are missing, the subscales will be missing. The subscale range for both anxiety and depression is 0 to 21.

Relation	Question	Response
Anxiety	I feel tense or 'wound up':	3=Most of the time; 2=A lot of the time; 1=From time to time; 0=Not at all
Depression	I still enjoy the things I used to enjoy:	0=Definitely as much; 1=Not quite so much; 2=Only a little; 3=Hardly at all
Anxiety	I get a sort of frightened feeling as if something awful is about to happen:	3=Very definitely and quite badly; 2=yes, but not too badly;1=a little, but it doesn't worry me; 0=Not at all
Depression	I can laugh and see the funny side of things:	0=As much as I always could; 1=Not quite so much now; 2=Definitely not so much now; 3=Not at all
Anxiety	Worrying thoughts go through my mind:	3=A great of the time; 2=A lot of the time, 1=From time to time, but not too often; 0=Only occasionally
Depression	I feel cheerful:	3=Not at all; 2=Not often; 1=Sometimes; 0=Most of the time
Anxiety	I can sit at ease and feel relaxed:	0=Definitely; 1=Usually; 2=Not often; 3=Not at all
Depression	I feel as if I am slowed down:	3=Nearly all the time; 2=Very often; 1=Sometimes; 0=Not at all
Anxiety	I get a sort of frightened feeling like 'butterflies' in the stomach:	0=Not at all; 1=Occasionally; 2=Quite often; 3=Very often
Depression	I have lost interest in my appearance:	3=Definitely; 2=I don't take as much care as I should; 1=I may not take quite as much care; 0=I take just as much care as ever
Anxiety	I feel restless as if I have to be on the move:	3=Very much indeed; 2=Quite a lot; 1=Not very much; 0=Not at all
Depression	I look forward with enjoyment to things:	0=As much as I ever did; 1=Rather less that I use to; 2=Definitely less than I use to; 3=Hardly at all

Relation	Question	Response
Anxiety	I get sudden feelings of panic:	3=Very often indeed; 2=Quite often; 1=Not very often; 0=Not at all
Depression	I can enjoy a good book or radio or TV program:	0=Often; 1=Sometimes; 2=Not often; 3=Very seldom

8.1.1.3. Calculation of Overactive Bladder Symptom Score

Response to OAB-SS questionnaires will be transformed to numeric scores according to the following table. Total score will be calculated as sum of respective scores if there are no missing response to the questionnaires.

Question	Response	Score
How many times do you typically urinate from waking in the morning until sleeping at night?	<=7	0
	8-14	1
	>=15	2
How many times do you typically wake up to urinate from sleeping at night until waking in the morning?	0	0
	1	1
	2	2
	>=3	3
How often do you have a sudden desire to urinate, which is difficult to defer?	Not at all	0
	Less than once a week	1
	Once a week or more	2
	About once a day	3
	2-4 times a day	4
	5 times a day or more	5
How often do you leak urine because you cannot defer the sudden desire to urinate?	Not at all	0
	Less than once a week	1
	Once a week or more	2
	About once a day	3
	2-4 times a day	4
	5 times a day or more	5

8.1.2. Safety Endpoints Derivation Details

8.1.2.1. Definition of Treatment-Emergent Adverse Events

TEAE will identified based on the following CRF data.

- Start Date

- Was it occurred BEFORE the start of Study Drug Administration?

Logic will be as follows:

Participation in the Open-Label Extension Study	**Start Date**	**Was it occurred BEFORE the start of Study Drug Administration?**	**TEAE?**
Yes	< Date of first dose of study drug in DB phase	Any	No
	= Date of first dose of study drug in DB phase	Before (DB)	No
		After (DB)	Yes
	> Date of first dose of study drug in DB phase and ≤ 14 days after the last dose of study drug in DB phase or the first dose of study drug in LT phase whichever is earlier	After (LT)	No
		Before (DB) or After (DB)	Yes
	> 14 days after the last dose of study drug in DB phase or the first dose of study drug in the LT phase whichever is earlier	Any	No
No	< Date of first dose of study drug in DB phase	Any	No
	= Date of first dose of study drug in DB phase	Before (DB)	No
		After (DB)	Yes
	> Date of first dose of study drug in DB phase and ≤ follow-up visit (Visit 8) or 14 days after the last dose of study drug whichever is earlier	Any	Yes
	> follow-up visit (Visit 8) or >14 days after the last dose of study drug whichever is earlier	Any	No

8.1.3. Reason of Exclusion from Analysis Sets

Reason for exclusion from each analysis set and those criteria are shown below.

8.1.3.1. All Enrolled Subjects

- Deviation to informed consent:
  Subjects who had informed consent related PDs (IC01, IC03, IC04, IC05, IC06 or IN02) defined in PD List.
- GCP violation
  Subjects who had PD SP11 defined in PD List.

8.1.3.2. All Randomized Subjects

- Not randomized
  Subjects who does not have the Randomization Date recorded.
- Deviation to informed consent:
  Subjects who had informed consent related PDs (IC01, IC03, IC04, IC05, IC06 or IN02) defined in PD List.
- GCP violation
  Subjects who had PD SP11 defined in PD List.

8.1.3.3. Safety Analysis Set

- Not treated:
  Subjects who did not have any data of receiving study drug administration.
- Deviation to informed consent:
  Subjects who had informed consent related PDs (IC01, IC03, IC04, IC05, IC06 or IN02) defined in PD List.
- GCP violation
  Subjects who had PD SP11 defined in PD List.

8.1.3.4. Modified Intent-to-Treat Analysis Set

- Not randomized
  Subjects who does not have the Randomization Date recorded.
- Not treated:
  Subjects who did not have any data of receiving study drug administration.
- Deviation to informed consent:
  Subjects who had informed consent related PDs (IC01, IC03, IC04, IC05, IC06 or IN02) defined in PD List.
- GCP violation
  Subjects who had PD SP11 defined in PD List.

8.1.3.5. Per-Protocol Set

- Not randomized
  Subjects who does not have the Randomization Date recorded.

- Not treated:
  Subjects who did not have any data of receiving study drug administration.
- Deviation to informed consent:
  Subjects who had informed consent related PDs (IC01, IC03, IC04, IC05, IC06 or IN02) defined in PD List.
- GCP violation
  Subjects who had PD SP11 defined in PD List.
- Deviation to eligibility criteria:
  Subjects who had eligibility criteria related PDs (deviations which start from IN or EX and the Actions to be Taken for Analysis is Exclude from PPS) defined in PD List.
- Deviation for investigational product:
  Subjects who had investigational product related PDs (deviations which start from IP and the Actions to be Taken for Analysis is Exclude from PPS) defined in PD List.
- Deviation for concomitant medications:
  Subjects who had concomitant medications related PDs (deviations which start from CM and the Actions to be Taken for Analysis is Exclude from PPS) defined in PD List.
- Deviation for study procedures:
  Subjects who had study procedures related PDs (deviations which start from SP and the Actions to be Taken for Analysis is Exclude from PPS) defined in PD List.

8.2. Data Handling Conventions

8.2.1. Definition and Use of Visit Windows

ADPS and ADSIS for each week will be calculated as described in Section 4.1.1. For data other than the diary data, summarization of the data displays and analysis conducted will use the visit number collected on the CRF, as the study schedule outlines (Table 3-1 and Table 3-2). Exceptions to this may occur when the subject early terminates and the date of the early termination visit is required to be mapped back to the most appropriate scheduled visit in order for proper summarization and analysis or when central laboratory or third party data does not contain scheduled visit information as in the case of an early termination, unscheduled visits or if the scheduled visit information is confirmed incorrect. In these instances, the data collected will be mapped to a scheduled intended visit for analysis and display purposes using the date of collection as a basis to determine study day and then study day will be mapped to the intended visit. The table below contains the study day windowing intervals. When more than one observation falls in a study day window, the available observation closest to the intended study day (ISD) will be used in the summary and analysis.

Study Day Window	Visit (V) / Week (W) / ISD	Visit Identification Mapped to
Day -14 to -7	V1 / Screening	Visit 1

Study Day Window	Visit (V) / Week (W) / ISD	Visit Identification Mapped to
Day 1	V2 / Baseline / ISD=1	Visit 2
Day 6 to 10	V3 / W1 / ISD=8	Visit 3
Day 13 to 17	V4 / W2 / ISD=15	Visit 4
Day 40 to 46	V5 / W6 / ISD=43	Visit 5
Day 68 to 74	V6 / W10 / ISD=71	Visit 6
Day 96 to 102	V7 / W14 / ISD=99	Visit 7
Day 5 to 14 post-last dose	V8 / W15 / ISD=Day of last dose + 7 days	Visit 8

For laboratory parameters, where scheduled visit data is missing or invalid and there exists an unscheduled sample drawn, if appropriate the unscheduled sample may take the place of the missing or invalid sample and be assigned to the scheduled visit for analysis purposes. For this situation, the above window scheduling will be applied. If multiple samples are available within the same window, the sample obtained on the day closest to the ISD should be selected. If there are two or more samples collected on days that are equidistant from the ISD, the sample collected later will be used for analysis.

8.2.2. Repeated or Unscheduled Assessments of Safety Parameters

Not applicable. Any specific handlings will be decided before database lock.

8.2.3. Handling of Missing Data

Missing AE onset date will be imputed for AEs occuring after the first dose of DB phase (i.e, "Was it occurred BEFORE the start of Study Drug Administration?" = After (DB)). AEs occuring before the first dose of DB phase of after the first dose of LT phase will be considered non-TEAE for DB phase, therefore AE onset date will not need to be imputed. Imputation will be performed according to the following rules:

- If only the day is missing and the month and year are the same as the month and year of first dosing of DB phase, the day will be imputed to the day of first dosing of DB phase; otherwise, the day will be imputed to the first day of the month.
- If both the day and month are missing and the year is the same as the year of the first dosing of DB phase, the day and month will be imputed to the day and month of the first dosing of DB phase; otherwise, the day and month will be imputed to the first of January.
- If the day is fully missing, the day will be imputed to the first dosing of DB phase.

If severity is missing for an AE occuring before the first dose of DB phase (i.e, "Was it occurred BEFORE the start of Study Drug Administration?" = Before (DB), then a severity of "mild" will be assigned. If severity is missing for an AE occuring after the first dose of DB phase (i.e, "Was it occurred BEFORE the start of Study Drug Administration?" = After (DB), then a severity of

"severe" will be assigned. The imputed values for the severity assessment will be used for incidence summaries, while the actual values will be used in data listings.
If the relationship to study treatment is missing for an AE occuring before the first dose of DB phase (i.e, "Was it occurred BEFORE the start of Study Drug Administration?" = Before (DB), then a relationship of "unrelated" will be assigned. If the relationship to study treatment is missing for an AE occuring after the first dose of DB phase (i.e, "Was it occurred BEFORE the start of Study Drug Administration?" = After (DB), a relationship of "related" will be assigned. The imputed values of relationship to double-blind study treatment will be used for incidence summaries, while the actual values will be presented in data listings.

8.2.4. Character Values of Clinical Laboratory Tests

Not applicable. Any specific handlings will be decided before database lock.

8.2.5. Handing of Below-Limit-of Quantification Values

Not applicable. Any specific handlings will be decided before database lock.

8.2.6. Reporting Unit

Clinical laboratory parameters will be converted and reported in the units shown in Table 8-2.

Table 8-2 Reporting Units for Clinical Laboratory Parameters

Assessment	Parameters	Unit
Hematology	Leukocytes	10^9/L
	Erythrocytes	10^{12}/L
	Hemoglobin	g/L
	Hematocrit	Fraction of 1
	Platelets (count)	10^9/L
	Neutrophils (count)	10^9/L and %
	Eosinophils (count)	10^9/L and %
	Basophils (count)	10^9/L and %
	Monocytes (count)	10^9/L and %
	Lymphocytes (count)	10^9/L and %
	Reticulocytes	%
Blood chemistry	Total protein	g/L
	Albumin	g/L
	Albumin/Globulin (A/G) ratio	Ratio
	T-Bil	µmol/L

Assessment	Parameters	Unit
	AST (GOT)	U/L
	ALT (GPT)	U/L
	ALP	U/L
	γ-GT (γ-GTP)	U/L
	LDH	U/L
	BUN	mmol/L
	Creatinine	μmol/L
	Uric acid	μmol/L
	Creatine kinase	U/L
	Total cholesterol	mmol/L
	Triglycerides	mmol/L
	Sodium (Na)	mmol/L
	Potassium (K)	mmol/L
	Chloride (Cl)	mmol/L
	Calcium (Ca)	mmol/L
	Magnesium (Mg)	mmol/L
	Phosphate (P)	mmol/L
	Bicarbonate	mmol/L
	C-Reactive Protein (CRP)	nmol/L
	CLcr	mL/min
Urinalysis	Specific gravity	Ratio
	pH	Null
	Protein	Null
	Glucose	Null
	Ketones	Null
	Urobilinogen	Null
	Occult blood	Null
	Leukocytes / WBC	/HPF
	Erythrocytes / RBC	/HPF

Assessment	Parameters	Unit
	Bilirubin	Null
HbA1c	HbA1c	%

8.2.7. SAS Program Code for Primary Analysis and Sensitivity Analyses

For the primary efficacy analysis (Section 7.2.1.1) and sensitivity analyses described in Sections 7.2.1.2.1, 7.2.1.3.1, and 7.2.1.3.2, the three SAS models will be used with the following macro parameters.

Module 1 (%MI_part1) for Generating Imputed Datasets

```
%MACRO mi_part1(
 dsetin =,   /* Dataset containing result */
 subset =,   /* subset on dsetin */
 dsetinpop =,   /* Dataset containing all covariates and population flags */
 pop =,      /* Population Flag */
 ctscovar =,     /* Continuous Covariates for imputation */
 catcovar =,     /* Categorical Covariates for imputation*/
 trtcd =,     /* Treatment Code Variable */
 trtgrp =,    /* Treatment Group Variable */
 mitype =,  /* Specify either PMI or DELTASHIFT */
 trunclow =,     /* Truncate results - lower limit, use -99999 or lower if no limit */
 truncup =,/* Truncate results - upper limit, use 99999 or higher if no limit */
 wdreas =,  /* Variable containing reason for discontinuation - Required for DELTASHIFT */
 shift =,           /* Variable containing shifts AE, LOE, AOR - Required for DELTASHIFT */
 mcmcseed =,  /* Seed for MCMC step */
 monoseed =,   /* Seed for REGPMM step */
 unifseed =,     /* Seed for uniform random number - Required for DELTASHIFT only */
 nimpute_mono =,/* Number of Imputations for monotone step */
 nimpute_nmar =,  /* Number of imputations for the NMAR step (delta shift or PMI) */
 regpmmk =,    /* Value of K in REGPMM */
 dsetout =, /* Output Dataset Name */
 titlno =,    /* Value of the title number for the indexes */
 control =,  /* Treatment Number of Control Group - Required for PMI*/
 prefix =,   /* Prefix for intermediate dataset names */
 tidyup =    /* Cleans library after use */
);

/*** Utility Macro ***/
%MACRO sqllist(string);
 %sysfunc(tranwrd(&string,%str( ), %str(, )))
%MEND;

/*
```

```
** Macro Variable Pre-processing
*/

%let all_covar = &ctscovar &catcovar;

%IF %nrbquote(&subset.) = %THEN %DO;
 %LET subset=1;
%END;

%LET nimpute_tot=%eval(&nimpute_mono.*&nimpute_nmar.);

/*****************************************************************************
********************************
***** Section 0 - Pre-processing *****
***** - Get Data *****
***** - Create indicators for Categorical Covariates *****
*****************************************************************************
********************************/

/* Get Data */
PROC SQL NOPRINT;
 CREATE TABLE &prefix.ds1 AS
 SELECT b.*, a.&trtcd., a.&trtgrp., a.paramn, a.paramcd, a.param, a.avisitn, a.avisit, a.aval,
a.chg, a.base, a.ablfl
 FROM
 (SELECT * FROM &dsetin. WHERE &subset.) AS a
 INNER JOIN
 (SELECT usubjid, %sqllist(&all_covar.), &pop., &wdreas.
 FROM &dsetinpop.
 WHERE &pop="Y") AS b
 ON a.usubjid=b.usubjid;
QUIT;

%if &syserr > 0 %then %return;

PROC SORT DATA=&prefix.ds1;
 BY usubjid &trtcd. &all_covar. avisitn;
RUN;

/*** Build in withdrawal reason ***/
DATA &prefix.ds1;
 SET &prefix.ds1;
 LENGTH miwd $4;
 /* If other conditions are required make change here and in delta shift section */
 IF upcase(&wdreas)="ADVERSE EVENT" THEN miwd="AE";
 ELSE IF upcase(&wdreas)="LACK OF EFFICACY" THEN miwd="LOE";
```

```
 /* Only subjects with non-missing data should be classified under any other reason */
 /* Subjects with truely missing data should not be shifted (ie MAR) */
 ELSE IF not missing(&wdreas) THEN miwd="AOR";
RUN;

/*** Need to know the length of the variable names for transreg to ensure variables are prefixed
with variable name ***/
%MACRO varlength;
 %GLOBAL varlen;
 DATA _null;
 varlen=
 %DO _i=1 %TO %SYSFUNC(countw(&trtcd. &catcovar.));
 PUT(%LENGTH(%SCAN(&trtcd. &catcovar.,&_i.)),1.) || " " ||
 %END; "";
 CALL SYMPUT("varlen",varlen);
 RUN;
 %IF &SYSERR > 0 %THEN %RETURN;
%MEND;
%VARLENGTH;

/*** Create indicator variables for classification variables ***/
PROC TRANSREG DATA=&prefix.ds1 DESIGN;
 MODEL class(&trtcd. &catcovar. / ZERO=first CPREFIX=&varlen.);
 ID usubjid &trtgrp. &wdreas. &ctscovar. avisit: aval chg base miwd ablfl;
 OUTPUT OUT=&prefix.ds2(DROP=_: Int: &catcovar);
RUN;

/* Create 1 to XX sequential ordered variable for visit number (to make processing easier!) */
PROC SORT DATA=&prefix.ds2;
 BY avisitn;
RUN;

DATA &prefix.ds2;
 SET &prefix.ds2;
 BY avisitn;
 RETAIN new_visno 0;
 IF first.avisitn THEN new_visno=new_visno+1;
RUN;

/*** Create new macro variable with new design matrix variables ***/
%MACRO design_covar;
%GLOBAL dscatcovar trtcovar;
 ODS SELECT NONE; /*suppress output*/
 ODS OUTPUT Position=_tmp_var;
 PROC CONTENTS DATA=&prefix.ds2 ORDER=VARNUM;
```

```
 RUN;
 ODS SELECT ALL;

 DATA _tmp_design1;
 SET _tmp_var END=eof;
 LENGTH macvar trtvar $1000.; /* DI update to 1000 characters to avoid truncation */
 RETAIN macvar trtvar;
 %DO i=1 %TO %sysfunc(countw(&catcovar.));
 IF index(upcase(variable),upcase("%scan(&catcovar.,&i,%str( ))")) > 0 THEN keepme&i=1;
 %END;
 IF max(of keepme:,0)=1 THEN macvar=catx(" ",macvar,variable);

 IF index(upcase(variable),upcase("&trtcd.")) > 0 and upcase("&trtcd.") ne upcase(variable)
THEN trtvar=catx(" ",trtvar,variable);
 IF eof THEN DO;
 CALL SYMPUT("dscatcovar", strip(macvar));
 CALL SYMPUT("trtcovar", strip(trtvar));
 END;
 RUN;
 %IF &SYSERR > 0 %THEN %RETURN;
%mend;
%design_covar;

/*****************************************************************************
********************************
***** Section 1 - Monotone Imputation *****
***** - Impute missing data using MAR assumption if not last visit *****
*****************************************************************************
******************************/

PROC SORT DATA=&prefix.ds2;
 BY usubjid &trtcovar &ctscovar &dscatcovar miwd;
RUN;

PROC TRANSPOSE DATA=&prefix.ds2 OUT=&prefix.ds3 PREFIX=vis;
 BY usubjid &trtcd &trtcovar &ctscovar &dscatcovar miwd;
 ID new_visno;
 IDLABEL avisit;
 VAR aval;
RUN;

/* Create dataset containing Avisitn and new_visno for seed selection later*/
PROC SQL NOPRINT;
 CREATE TABLE _tmp_new_visno AS SELECT DISTINCT avisitn, new_visno FROM
&prefix.ds2;
QUIT;
```

```
/*** Look at missingness pattern ***/
TITLE&titlno. J=L "###1### - Missingness Pattern";
PROC MI DATA=&prefix.ds3 NIMPUTE=0;
 VAR vis:;
RUN;


/*** Impute Monotone Missingness Pattern ***/
TITLE&titlno. J=L "###2### - Monotone Imputation";
PROC MI DATA=&prefix.ds3 NIMPUTE=&nimpute_mono SEED=&mcmcseed
OUT=&prefix.ds4;
 MCMC IMPUTE=monotone;
 VAR &trtcovar &dscatcovar &ctscovar vis:;
RUN;

/*** Need Macro variable for maximum visit ***/
PROC SQL NOPRINT;
 SELECT compress(put(max(new_visno),8.0)) INTO: maxvis FROM &prefix.ds2;
QUIT;

/*** Create Variable with missing data pattern (for looping and further processing) ***/
DATA &prefix.ds4;
 SET &prefix.ds4;
 %IF &nimpute_mono=1 %THEN %DO;
 monoimp=1;
 %END;
 %ELSE %DO;
 /* rename _imputation_ variable to allow for next NMAR imputations */
 RENAME _imputation_=monoimp;
 %END;

 ARRAY vis [&maxvis] vis1-vis&maxvis.;
 DO i=&maxvis. TO 1 BY -1;
 IF vis[i]=. THEN misspatt = i;
 /* Any values imputed outside limits should be set to limits */
 IF vis[i] > &truncup. THEN vis[i]=&truncup.;
 IF vis[i] < &trunclow. and not missing(vis[i]) THEN vis[i]=&trunclow.;
 END;
RUN;
%IF &SYSERR > 0 %THEN %RETURN;

/* For next steps make duplicates of the monotone data to make final data structure (ie 1 NMAR
imputation only) */
DATA &prefix.ds5;
 SET &prefix.ds4;
```

```
 DO i=1 TO &nimpute_nmar;
 _imputation_=((monoimp-1)*&nimpute_nmar)+i;
 OUTPUT;
 END;
RUN;

PROC SQL NOPRINT;
 SELECT compress(put(min(misspatt),8.0)) INTO: start FROM &prefix.ds4;
QUIT;

/***
**** Initialise first dataset in loop - Same for REGPMM and PMI
**** This is the first visit with missing data (otherwise errors will occur with MI).
**** Sort order into PROC MI is important.
***/

PROC SORT DATA=&prefix.ds5 OUT=&prefix.ds5_%EVAL(&start-1);
 BY _imputation_ usubjid misspatt;
RUN;
%IF &SYSERR > 0 %THEN %RETURN;


/*****************************************************************************
*********************************
***** Section 2a - Delta Shift *****
*****************************************************************************
*******************************/

%MACRO run_deltashift;

/* Loop through all visits with missing data */
%DO j=&start. %TO &maxvis.;

 %IF &SYSERR > 0 %THEN %RETURN;

 /* Macro Variable for previous visit */
 %LET k=%EVAL(&j-1);

 PROC SORT DATA=&prefix.ds5_&k;
 BY _Imputation_ usubjid;
 RUN;

 /* Present only the first and last imputation to save output space */
 ODS SELECT WHERE=(index(lowcase(_path_),".bygroup1.") or
index(lowcase(_path_),".bygroup&nimpute_tot."));
```

```
 TITLE&titlno. J=L "###3### - Delta Shift - MI";
 /* Use PROC MI with all previous visits to impute data only require 1 imputation (MCMC step
has all imputations) */
 PROC MI DATA=&prefix.ds5_&k NIMPUTE=1 SEED=&monoseed.
OUT=&prefix.ds5_&j._mi;
 BY _Imputation_;
 MONOTONE regpmm(vis&j= &trtcovar &dscatcovar &ctscovar %DO i=1 %TO &k;
vis&i. %END; / k=&regpmmk);
 VAR &trtcovar &dscatcovar &ctscovar %DO i=1 %TO &j; vis&i. %END;;
 RUN;

 /* Present only the first and last imputation to save output space */
 ODS SELECT WHERE=(index(lowcase(_path_),".bygroup1.") or
index(lowcase(_path_),".bygroup&nimpute_tot."));

 TITLE&titlno. J=L "###4### - Delta Shift - RSD";
 /*** Calculate Residual Standard Deviation ***/
 PROC MIXED DATA=&prefix.ds5_&j._mi ;
 BY _Imputation_;
 CLASS &trtcd;
 MODEL vis&j. = &trtcd %DO i=1 %TO &k; vis&i. %END; / NOTEST;
 ODS OUTPUT CovParms=&prefix.ds5_&j._rsd(rename=(estimate=rvarvis&j.) drop=covparm);
 RUN;

 ODS SELECT ALL;

 /* Create macro variable with visit number in to create seed */
 DATA _null_;
 SET _tmp_new_visno;
 IF new_visno=&j. THEN CALL SYMPUT("avisno",compress(put(avisitn,8.0)));
 RUN;

 /* Merge on RSD and apply the shifting */
 DATA &prefix.ds5_&j.;
 MERGE &prefix.ds5_&j._mi
 &prefix.ds5_&j._rsd;
 BY _Imputation_;
 rsdvis&j.=sqrt(rvarvis&j.);
 /* Apply Shifting for first missing visit - Requires Truncating to 10 if greater*/
 IF misspatt = &j THEN DO;
 IF miwd="AE" THEN vis&j=max(&trunclow., min(&truncup.,
vis&j+(%scan(&shift,1,%str( ))*rsdvis&j.*RANUNI(%sysevalf(&unifseed.+&avisno.)))));
 ELSE IF miwd="LOE" THEN vis&j=max(&trunclow., min(&truncup.,
vis&j+(%scan(&shift,2,%str( ))*rsdvis&j.*RANUNI(%sysevalf(&unifseed.+&avisno.)))));
 ELSE IF miwd="AOR" THEN vis&j=max(&trunclow., min(&truncup.,
vis&j+(%scan(&shift,3,%str( ))*rsdvis&j.*RANUNI(%sysevalf(&unifseed.+&avisno.)))));
```

```
 END;
 /* Check if LOE whether value is less than baseline visit (ie improvement) change it if it is */
 IF miwd="LOE" and misspatt le &j THEN vis&j=max(vis1, vis&j);
 RUN;
%END;

%IF &SYSERR > 0 %THEN %RETURN;

%MEND;

/*****************************************************************************
********************************
***** Section 2b - Placebo Multiple Imputation *****
*****************************************************************************
********************************/

%MACRO run_pmi;
 %DO j=&start. %TO &maxvis.;

 %IF &SYSERR > 0 %THEN %RETURN;
 /* Macro Variable for previous visitr */
 %LET k=%EVAL(&j-1);

 /* Split Data - Placebo + Treatment Variables with missing information at the visit of interest */
 DATA &prefix.ds5_&k._a
 &prefix.ds5_&k._b;
 SET &prefix.ds5_&k;
 IF &trtcd=&control or 1 le misspatt le &j THEN OUTPUT &prefix.ds5_&k._a;
 ELSE OUTPUT &prefix.ds5_&k._b;
 RUN;

 /* Present only the first and last imputation to save output space */
 ODS SELECT WHERE=(index(lowcase(_path_),".bygroup1.") or
index(lowcase(_path_),".bygroup&nimpute_tot."));

 /* Run PROC MI on just Control Data and Missing Data - No Treatment Variable */
 TITLE&titlno. J=L "###3### - Placebo Multiple Imputation";
 PROC MI DATA=&prefix.ds5_&k._a NIMPUTE=1 SEED=&monoseed.
OUT=&prefix.ds5_&j._mi;
 BY _Imputation_;
 MONOTONE regpmm(vis&j=&dscatcovar &ctscovar %DO i=1 %TO &k %BY 1;
vis&i. %END;);
 VAR &dscatcovar &ctscovar %DO i=1 %TO &j; vis&i. %END;;
 RUN;

 ODS SELECT ALL;
```

```
 /* Merge back on Data not imputed yet, so we are back to start */
 DATA &prefix.ds5_&j.;
 SET &prefix.ds5_&j._mi
 &prefix.ds5_&k._b;
 BY _imputation_ usubjid;
 RUN;

 %IF &SYSERR > 0 %THEN %RETURN;
 %END;

 %IF &SYSERR > 0 %THEN %RETURN;

%MEND;

/*****************************************************************************
********************************
***** Section 2c - pMI + Delta Shift *****
*****************************************************************************
********************************/

%MACRO run_deltashift_pmi;

/* Loop through all visits with missing data */
%DO j=&start. %TO &maxvis.;

 %IF &SYSERR > 0 %THEN %RETURN;

 /* Macro Variable for previous visit */
 %LET k=%EVAL(&j-1);

 PROC SORT DATA=&prefix.ds5_&k;
 BY _Imputation_ usubjid;
 RUN;

 /* Present only the first and last imputation to save output space */
 ODS SELECT WHERE=(index(lowcase(_path_),".bygroup1.") or
index(lowcase(_path_),".bygroup&nimpute_tot."));

 TITLE&titlno. J=L "###3### - pMI + Delta Shift - MI";
 /* Use PROC MI with all previous visits to impute data only require 1 imputation (MCMC step
has all imputations) */
 PROC MI DATA=&prefix.ds5_&k NIMPUTE=1 SEED=&monoseed.
OUT=&prefix.ds5_&j._mi;
 BY _Imputation_;
 CLASS &trtcd;
```

```
 MONOTONE regpmm(vis&j= &dscatcovar &ctscovar %DO i=1 %TO &k; vis&i. %END; /
k=&regpmmk);
 MNAR MODEL(vis&j / modelobs=(&trtcd="&control"));
 VAR &trtcovar &dscatcovar &ctscovar %DO i=1 %TO &j; vis&i. %END;;
 RUN;

 /* Present only the first and last imputation to save output space */
 ODS SELECT WHERE=(index(lowcase(_path_),".bygroup1.") or
index(lowcase(_path_),".bygroup&nimpute_tot."));

 TITLE&titlno. J=L "###4### - pMI + Delta Shift - RSD";
 /*** Calculate Residual Standard Deviation ***/
 PROC MIXED DATA=&prefix.ds5_&j._mi ;
 BY _Imputation_;
 CLASS &trtcd;
 MODEL vis&j. = &trtcd %DO i=1 %TO &k; vis&i. %END; / NOTEST;
 ODS OUTPUT CovParms=&prefix.ds5_&j._rsd(rename=(estimate=rvarvis&j.) drop=covparm);
 RUN;

 ODS SELECT ALL;

 /* Create macro variable with visit number in to create seed */
 DATA _null_;
 SET _tmp_new_visno;
 IF new_visno=&j. THEN CALL SYMPUT("avisno",compress(put(avisitn,8.0)));
 RUN;

 /* Merge on RSD and apply the shifting */
 DATA &prefix.ds5_&j.;
 MERGE &prefix.ds5_&j._mi
 &prefix.ds5_&j._rsd;
 BY _Imputation_;
 rsdvis&j.=sqrt(rvarvis&j.);
 /* Apply Shifting for first missing visit - Requires Truncating to 10 if greater*/
 IF misspatt = &j THEN DO;
 IF miwd="AE" THEN vis&j=max(&trunclow., min(&truncup.,
vis&j+(%scan(&shift,1,%str( ))*rsdvis&j.*RANUNI(%sysevalf(&unifseed.+&avisno.)))));
 ELSE IF miwd="LOE" THEN vis&j=max(&trunclow., min(&truncup.,
vis&j+(%scan(&shift,2,%str( ))*rsdvis&j.*RANUNI(%sysevalf(&unifseed.+&avisno.)))));
 ELSE IF miwd="AOR" THEN vis&j=max(&trunclow., min(&truncup.,
vis&j+(%scan(&shift,3,%str( ))*rsdvis&j.*RANUNI(%sysevalf(&unifseed.+&avisno.)))));
 END;
 /* Check if LOE whether value is less than baseline visit (ie improvement) change it if it is */
 IF miwd="LOE" and misspatt le &j THEN vis&j=max(vis1, vis&j);
 RUN;
%END;
```

```
%IF &SYSERR > 0 %THEN %RETURN;

%MEND;

/* Run required method */
%IF %UPCASE(&mitype)=DELTASHIFT %THEN %DO;
 %run_DELTASHIFT;
%END;
%ELSE %IF %UPCASE(&mitype)=PMI %THEN %DO;
 %run_pmi;
%END;
%ELSE %IF %UPCASE(&mitype)=DELTASHIFT_PMI %THEN %DO;
 %run_deltashift_pmi;
%END;

/*****************************************************************************
********************************
***** Section 3 - Postprocessing *****
*****************************************************************************
*******************************/

/* Recalculate CFB - Transpose to Long/Thin and merge on baseline */
PROC SORT DATA=&prefix.ds5_&maxvis.;
 BY usubjid _imputation_ misspatt miwd;
RUN;

PROC TRANSPOSE DATA=&prefix.ds5_&maxvis. OUT=&prefix.ds6_1;
 BY usubjid _imputation_ misspatt miwd;
 VAR vis:;
RUN;

/* Get Covariate Information and merge back on */
PROC SQL NOPRINT;
 CREATE TABLE &prefix.ds6_2 AS
 SELECT b.*, a._imputation_, a.misspatt, input(tranwrd(_name_,"vis",""),best.) as new_visno,
a.aval
 FROM &prefix.ds6_1 AS a
 INNER JOIN
 (SELECT DISTINCT usubjid, %sqllist(&all_covar.), &trtcd., &trtgrp., base
 FROM &prefix.ds1
 ) AS b
 ON a.usubjid=b.usubjid
 ORDER BY _imputation_, usubjid, new_visno;

 /* Merge on Visit Information from &prefix.ds2 */
```

```
 CREATE TABLE &dsetout. AS
 SELECT a.*, a.aval - a.base as chg, b.avisitn, b.avisit, b.ablfl
 FROM &prefix.ds6_2 as a
 LEFT JOIN
 (SELECT DISTINCT new_visno, avisitn, avisit, ablfl FROM &prefix.ds2) as b
 ON a.new_visno=b.new_visno
 ORDER BY _imputation_, usubjid, avisitn;
QUIT;

%IF %UPCASE(&tidyup)=Y %THEN %DO;
 PROC DATASETS LIBRARY=WORK MEMTYPE=DATA;
 DELETE &prefix.ds: _tmp: ;
 QUIT;
%END;

********* END OF MACRO **********;
%IF &SYSERR > 0 %THEN %RETURN;
%MEND;
```

Module 2 (%MI_part2) for MMRM Analysis

```
%MACRO mi_part2(
 dsetin =,   /* Dataset containing imputated data */
 subset =,   /* subset on dsetin */
 impvar =, /* name of variable containing numeric imputation variable (_imputation_ not an
ADaM variable) */
 dsetinpop =,   /* Dataset containing all covariates and population flags - 1 row per subject */
 pop =,      /* Population Flag - incase further subsetting needing to be done on primary dataset*/
 analysis =,     /* MMRM or ANCOVA */
 byvar = ,   /* By variable for analysis e.g. AVISITN or SUBGROUP*/
 mixedcovs =, /* Continuous Covariates for inclusion in Proc Mixed */
 mixedclass =, /* Categorical Class Covariates for inclusion in Proc Mixed */
 trtcd =,     /* Treatment Code Variable */
 trtgrp =,    /* Treatment Group Variable */
 invertdiffs =,  /* Invert Differences if control group(s) are lower numbers than active */
 ddfm =,    /* Specification of denominator degrees of freedom K-R is very slow!*/
 covar_str =,    /* Specification of covariance stucture */
 suffix =,   /* prefix for Output datasets to enable parralisation of code */
 outlib =    /* Library for output datasets - for batch running */
 );

/* Utility Macro */
%MACRO sqllist(string);
 %sysfunc(tranwrd(&string,%str( ), %str(, )))
%MEND;
```

```
/*
** Macro Variable Pre-processing
*/

%IF %upcase(&byvar)=AVISITN %THEN
 %LET all_covar = %cmpres(&mixedcovs &mixedclass);
%ELSE %LET all_covar = %cmpres(&byvar &mixedcovs &mixedclass);

%IF %nrbquote(&subset.) = %THEN %DO;
 %LET subset=1;
%END;

/*
** Get Data
*/
PROC SQL NOPRINT;
 CREATE TABLE ds1 AS
 SELECT b.*, a.&impvar as _imputation_, &trtcd., &trtgrp., a.avisitn, a.avisit, a.aval, a.chg,
a.base
 FROM
 (SELECT * FROM &dsetin. WHERE &subset.) AS a
 INNER JOIN
 (SELECT usubjid, %IF %nrbquote(&all_covar.) ne %THEN %sqllist(&all_covar.),; &pop.
 FROM &dsetinpop.
 WHERE &pop="Y") AS b
 ON a.usubjid=b.usubjid;
QUIT;

/* Get lists of visits */
PROC SQL NOPRINT;
 SELECT DISTINCT AVISITN INTO: all_vis SEPARATED BY " " FROM ds1;
 SELECT DISTINCT max(_imputation_) INTO: nimpute_tot FROM ds1;
 SELECT DISTINCT min(_imputation_) INTO: nimpute_min FROM ds1;
QUIT;

%IF %UPCASE(&analysis)=MMRM %THEN %DO;

 PROC SORT DATA=ds1;
 BY _imputation_ &byvar. usubjid &trtcd. &all_covar. avisitn;
 RUN;

 /* Loop through and get estimates for parameters as initial values */
 %LET converge=1;
 %LET i=&nimpute_min.;

 /* Initial Values for CHG */
```

```
%DO %WHILE (&converge. gt 0 NO and &i le &nimpute_tot.);
PROC MIXED DATA=ds1(where=(_imputation_=&i.)) PLOTS=NONE NOCLPRINT;
BY _imputation_ &byvar.;
CLASS &trtcd &mixedclass. avisitn usubjid;
MODEL chg = &trtcd. avisitn &trtcd*avisitn base &mixedcovs. &mixedclass. /
DDFM=&ddfm. NOTEST;
REPEATED avisitn / Subject=usubjid TYPE=&covar_str.;
ODS OUTPUT ConvergenceStatus=cs
covparms=cp_chg;
RUN;

PROC SQL NOPRINT;
SELECT max(status) INTO: converge FROM cs;
QUIT;
%LET i=%eval(&i+1);
%END;

%LET converge=1;
%LET i=&nimpute_min.;

/* Initial Values for AVAL */
%DO %WHILE (&converge. gt 0 NO and &i le &nimpute_tot.);
PROC MIXED DATA=ds1(where=(_imputation_=&i.)) PLOTS=NONE NOCLPRINT;
BY _imputation_ &byvar.;
CLASS &trtcd &mixedclass. avisitn usubjid;
MODEL aval = &trtcd. avisitn &trtcd*avisitn base &mixedcovs. &mixedclass. /
DDFM=&ddfm. NOTEST;
REPEATED avisitn / Subject=usubjid TYPE=&covar_str.;
ODS OUTPUT ConvergenceStatus=cs
covparms=cp_aval;
RUN;

PROC SQL NOPRINT;
SELECT max(status) INTO: converge FROM cs;
QUIT;
%LET i=%eval(&i+1);
%END;

DATA cp_aval_all;
SET cp_aval(drop=_imputation_);
DO _imputation_=&nimpute_min. TO &nimpute_tot.;
OUTPUT;
END;
RUN;

PROC SORT DATA=cp_aval_all;
```

```
BY _imputation_ &byvar.;
RUN;

DATA cp_chg_all;
SET cp_chg(drop=_imputation_);
DO _imputation_=&nimpute_min. TO &nimpute_tot.;
OUTPUT;
END;
RUN;

PROC SORT DATA=cp_chg_all;
BY _imputation_ &byvar.;
RUN;


/* Because of amount of output generated only show the proc mixed output for first and last
imputation*/
ODS SELECT WHERE=(index(lowcase(_path_),".bygroup1.") or
index(lowcase(_path_),".bygroup%cmpres(&nimpute_tot.)"));
/* Perform MMRM Analysis by Imputation - Change from Baseline*/
PROC MIXED DATA=ds1 PLOTS=NONE NOCLPRINT;
BY _imputation_ &byvar.;
CLASS &trtcd &mixedclass. avisitn usubjid;
MODEL chg = &trtcd. avisitn &trtcd*avisitn base &mixedcovs. &mixedclass. /
DDFM=&ddfm. NOTEST;
REPEATED avisitn / Subject=usubjid TYPE=&covar_str.;
LSMEANS &trtcd*avisitn / DIFF CL;
PARMS / PARMSDATA=cp_chg_all;
ODS OUTPUT lsmeans=&outlib..lsm_chg&suffix.
diffs=&outlib..lsm_diffs&suffix.;
RUN;

ODS SELECT WHERE=(index(lowcase(_path_),".bygroup1.") or
index(lowcase(_path_),".bygroup%cmpres(&nimpute_tot.)"));
/* Perform MMRM Analysis by Imputation - Raw Analysis Value*/
PROC MIXED DATA=ds1 PLOTS=NONE NOCLPRINT;
BY _imputation_ &byvar.;
CLASS &trtcd &mixedclass. avisitn usubjid;
MODEL aval = &trtcd. avisitn &trtcd*avisitn base &mixedcovs. &mixedclass. /
DDFM=&ddfm. NOTEST;
REPEATED avisitn / Subject=usubjid TYPE=&covar_str.;
LSMEANS &trtcd*avisitn / CL;
PARMS / PARMSDATA=cp_aval_all;
ODS OUTPUT lsmeans=&outlib..lsm_aval&suffix.;
RUN;
```

```
 ODS SELECT ALL;
%END;

%IF %UPCASE(&analysis)=ANCOVA %THEN %DO;
 PROC SORT DATA=ds1;
 BY _imputation_ &byvar. usubjid &trtcd. &all_covar. ;
 RUN;

 /* Because of amount of output generated only show the proc mixed output for first and last
imputation*/
 ODS SELECT WHERE=(index(lowcase(_path_),".bygroup1.") or
index(lowcase(_path_),".bygroup%cmpres(&nimpute_tot.)"));
 /* Perform ANCOVA Analysis by Imputation - Change from Baseline*/
 PROC MIXED DATA=ds1 PLOTS=NONE NOCLPRINT;
 BY _imputation_ &byvar.;
 CLASS &trtcd &mixedclass. usubjid;
 MODEL chg = &trtcd. base &mixedcovs. &mixedclass. / DDFM=&ddfm. NOTEST;
 LSMEANS &trtcd / DIFF CL;
 ODS OUTPUT lsmeans=&outlib..lsm_chg&suffix.
 diffs=&outlib..lsm_diffs&suffix.;
 RUN;

 ODS SELECT WHERE=(index(lowcase(_path_),".bygroup1.") or
index(lowcase(_path_),".bygroup%cmpres(&nimpute_tot.)"));
 /* Perform ANCOVA Analysis by Imputation - Raw Analysis Value*/
 PROC MIXED DATA=ds1 PLOTS=NONE NOCLPRINT;
 BY _imputation_ &byvar.;
 CLASS &trtcd &mixedclass. usubjid;
 MODEL aval = &trtcd. base &mixedcovs. &mixedclass. / DDFM=&ddfm. NOTEST;
 LSMEANS &trtcd / CL;
 ODS OUTPUT lsmeans=&outlib..lsm_aval&suffix.;
 RUN;

 ODS SELECT ALL;
%END;

%IF %UPCASE(&invertdiffs)=Y %THEN %DO;
 /* By Defaul Proc Mixed uses last levels as controls if control level is lower than comparison
this should be inverted */
 DATA &outlib..lsm_diffs&suffix.(drop=old_:);
 SET &outlib..lsm_diffs&suffix.(rename=(lower=old_low upper=old_up estimate=old_est
&trtcd.=old_&trtcd. _&trtcd.=old__&trtcd.));
 estimate=-old_est;
 lower = -old_up;
 upper = -old_low;
 &trtcd. = old__&trtcd.;
```

```
 _&trtcd. = old_&trtcd.;
 RUN;
%END;

********* END OF MACRO **********;

%MEND;
```

Module 3 (%MI_part3) for Summary using Rubin's Rule

```
%MACRO MI_part3(
 inaval =,   /* Dataset name of LSMeans for Raw Value - Leave blank if not required */
 inchg =,    /* Dataset name of LSMeans for Change from Baseline - Leave blank if not
required */
 indiffs =,  /* Dataset name of LSMeans for Differences - Leave blank if not required */
 trtcd =,    /* Name of treatment variable */
 byvars =,   /* Name of by variables (e.g. for MMRM this would be avisitn) */
 adjdf =     /* Make small sample adjustment to degrees of freedom - Y or N only */
 );

DATA &indiffs.;
SET &indiffs.;
IF VNAMEX('avisitn')^=" AND VNAMEX('_avisitn')^=" THEN DO;
 IF avisitn=_avisitn and _trt01pn=1;
END;
ELSE DO;
 IF _trt01pn=1;
 avisitn=.;
 _avisitn=.;
END;
RUN;
/*** Utility Macro ***/
%MACRO sqllist(string);
 %sysfunc(tranwrd(&string,%str( ), %str(, )))
%MEND;

/* Looping macro (to process each dataset individually */
%MACRO analyze_me(
 a_dsetin=,
 a_byvars=
 );

 /* For small sample adjustment to DF we need to know what the maximum degrees of freedom
for each comparison of interest */
 PROC SQL NOPRINT;
 CREATE TABLE _tmp_df AS
```

```
SELECT %sqllist(&a_byvars), MAX(DF) as maxdf
FROM &a_dsetin.
GROUP BY %sqllist(&a_byvars)
ORDER BY %sqllist(&a_byvars);
QUIT;

/* Store DF in macro variables for each comparison */
DATA _null_;
SET _tmp_df END=EOF;
CALL SYMPUT(catx("_", "df", %sqllist(&a_byvars)), maxdf);
IF eof THEN CALL SYMPUT ("ncomp", compress(put(_n_,8.0)));
RUN;

/* Sort dataset */
PROC SORT DATA=&a_dsetin.;
BY &a_byvars. ;
RUN;

%LET cnt = %SYSFUNC(countw(&a_byvars," "));

%DO i=1 %TO &ncomp.;
/* For each comparison create macro variables with where clause and name of macro variable
for DF */
DATA _null_;
SET _tmp_df;
IF _n_=&i THEN DO;
CALL SYMPUT("getdata",
%DO j=1 %TO &cnt;
%IF &j=1 %THEN %DO; "%scan(&a_byvars., &j)=" || compress(put(%scan(&a_byvars., &j),
best8.)) %END;
%ELSE %DO;|| " and %scan(&a_byvars., &j)=" || compress(put(%scan(&a_byvars., &j),
best8.)) %END;
%END;
);
CALL SYMPUT("getdf", catx("_", "df", %sqllist(&a_byvars)));
END;
RUN;

/* Run Proc MIANALYZE with the option of adjusting degrees of freedom */
PROC MIANALYZE
DATA=&a_dsetin(WHERE=(&getdata.)) %IF %UPCASE(&adjdf)=Y %THEN
EDF=&&&getdf;;
BY &a_byvars;
MODELEFFECTS estimate;
STDERR stderr;
ODS OUTPUT ParameterEstimates=_tmp_&a_dsetin._&i;
```

```
RUN;
%END;

/* Set all datasets together */
DATA adj_&a_dsetin.;
SET _tmp_&a_dsetin._:;
BY &a_byvars;
RUN;

/* Remove all temporary datasets */
PROC DATASETS LIBRARY=WORK NOLIST NODETAILS NOWARN;
DELETE _tmp_:;
QUIT;

%MEND; /* Close loop macro */

%IF %SYSFUNC(EXIST(&inaval.)) AND &inaval.
ne %THEN %analyze_me(a_dsetin=&inaval., a_byvars=&byvars &trtcd.);;
%IF %SYSFUNC(EXIST(&inchg.)) AND &inchg.
ne %THEN %analyze_me(a_dsetin=&inchg., a_byvars=&byvars &trtcd.);;
%IF %SYSFUNC(EXIST(&indiffs.)) AND &indiffs.
ne %THEN %analyze_me(a_dsetin=&indiffs., a_byvars=&byvars &trtcd. _&trtcd.);;

********* END OF MACRO **********;

%MEND;
```

Macro Parameters for Analyses

The following macro parameters will be used for the analyses.

	Section 7.2.1.1 (primary)	Section 7.2.1.2.1 (different shift)	Section 7.2.1.3.1 (PPS)	Section 7.2.1.3.2 (placebo MI)
%MI_part1				
dsetin	adeff	adeff	adeff	adeff
subset	%str(((AVISITN=1002 and ABLFL="Y") or (1003 le AVISITN le 1016)) and dtype="AVERAGE" and PARAMCD="PI0107" and ANL01FL="Y")	%str(((AVISITN=1002 and ABLFL="Y") or (1003 le AVISITN le 1016)) and dtype="AVERAGE" and PARAMCD="PI0107" and ANL01FL="Y")	%str(((AVISITN=1002 and ABLFL="Y") or (1003 le AVISITN le 1016)) and dtype="AVERAGE" and PARAMCD="PI0107" and ANL01FL="Y")	%str(((AVISITN=1002 and ABLFL="Y") or (1003 le AVISITN le 1016)) and dtype="AVERAGE" and PARAMCD="PI0107" and ANL01FL="Y")
dsetinpop	adsl	adsl	adsl	adsl
pop	mittfl	mittfl	pprotfl	mittfl
ctscovar	NA	NA	NA	NA
catcovar	sexn agegr6n	sexn agegr6n	sexn agegr6n	sexn agegr6n

	Section 7.2.1.1 (primary)	Section 7.2.1.2.1 (different shift)	Section 7.2.1.3.1 (PPS)	Section 7.2.1.3.2 (placebo MI)
trtcd	trt01pn	trt01pn	trt01pn	trt01pn
trtgrp	trt01p	trt01p	trt01p	trt01p
mitype	DELTASHIFT_PMI	DELTASHIFT_PMI	DELTASHIFT_PMI	PMI
trunclow	0	0	0	0
truncup	10	10	10	10
wdreas	dcsreas	dcsreas	dcsreas	dcsreas
shift	1.0 1.0 0.5	0 0 0, 3.0 3.0 1.5, 5.0 5.0 2.5	1.0 1.0 0.5	NA
mcmcseed	627522	223784, 278650, 978027	897663	815639
monoseed	547462	841137, 035208, 134233	025670	952602
unifseed	703969	111412, 432894, 943449	184068	594926
nimpute_mono	1	1	1	1
nimpute_nmar	1000	1000	1000	1000
regpmmk	5	5	5	5
dsetout	adeff_mi	adeff_mi	adeff_mi	adeff_mi
titlno	4	4	4	4
control	1	1	1	1
prefix	_mip1_	_mip1_	_mip1_	_mip1_
tidyup	Y	Y	Y	Y
%MI_part2				
dsetin	adeff_mi	adeff_mi	adeff_mi	adeff_mi
subset	avisitn eq 1016	avisitn eq 1016	avisitn eq 1016	avisitn eq 1016
impvar	_imputation_	_imputation_	_imputation_	_imputation_
dsetinpop	adsl	adsl	adsl	adsl
pop	mittfl	mittfl	mittfl	mittfl
analysis	ANCOVA	ANCOVA	ANCOVA	ANCOVA
byvar	NA	NA	NA	NA
mixedcovs	NA	NA	NA	NA
mixedclass	NA	NA	NA	NA
trtcd	trt01pn	trt01pn	trt01pn	trt01pn
trtgrp	trt01p	trt01p	trt01p	trt01p
invertdiffs	Y	Y	Y	Y
ddfm	SAT	SAT	SAT	SAT
covar_str	UN	UN	UN	UN
suffix	NA	NA	NA	NA
outlib	work	work	work	work
%MI_part3				
inaval	lsm_aval	lsm_aval	lsm_aval	lsm_aval
inchg	lsm_chg	lsm_chg	lsm_chg	lsm_chg
indiffs	lsm_diffs	lsm_diffs	lsm_diffs	lsm_diffs
trtcd	trt01pn	trt01pn	trt01pn	trt01pn
byvars	NA	NA	NA	NA

	Section 7.2.1.1 (primary)	Section 7.2.1.2.1 (different shift)	Section 7.2.1.3.1 (PPS)	Section 7.2.1.3.2 (placebo MI)
adjdf	N	N	N	N

8.3. Statistical Summary and General Reporting Conventions

8.3.1. Computing Methods

All statistical analyses will be performed using Statistical Analysis System (SAS)® Version 9.4 or higher (SAS Institute, Cary, NC 27513).

8.3.2. Statistical Summary Conventions

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

8.3.3. General Reporting Conventions

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.

9. SUMMARY OF CHANGES TO THE STATISTICAL ANALYSES SPECIFIED IN PROTOCOL

No changes have been issued or planned.

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11. APPENDICES

Not applicable.