

Title: A Japan Post-marketing, Randomized, Double-blind, Parallel-group, Flexible Dose Comparative Study to Assess the Non-inferiority of Duloxetine Compared with Pregabalin in Patients with Diabetic Peripheral Neuropathic Pain.

NCT ID: NCT02417935

Document Approval Date: 02 Jun 2017

1. Statistical Analysis Plan for Study F1J-JE-HMHA:

A Japan Post-marketing, Randomized, Double-blind, Parallel- group, Flexible Dose Comparative Study to Assess the Non- inferiority of Duloxetine Compared with Pregabalin in Patients with Diabetic Peripheral Neuropathic Pain

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LY248686 (Duloxetine Hydrochloride)

Study F1J-JE-HMHA (1413N0841) will be a post-marketing, Phase 4, multicenter, randomized, double-blind, parallel-group, flexible-dose, comparative study to assess the non-inferiority of duloxetine (40 to 60 mg/day) compared with pregabalin (300 to 600 mg/day) for 12 weeks in adult outpatients with diabetic peripheral neuropathic pain.

Eli Lilly Japan K.K.
Protocol F1J-JE-HMHA
Phase 4

Statistical Analysis Plan electronically signed and approved by Lilly on date provided below.

Approval Date: 02 Jun 2017

2. Table of Contents

Section	Page
1. Statistical Analysis Plan for Study F1J-JE-HMHA:	1
2. Table of Contents	2
3. Revision History	4
4. Study Objectives	5
4.1. Primary Objective	5
4.2. Secondary Objectives	5
5. Study Design	6
6. A Priori Statistical Methods	8
6.1. Determination of Sample Size	8
6.2. General Considerations	8
6.3. Handling of Dropouts or Missing Data	9
6.3.1. Baseline Observation Carried Forward	9
6.3.2. Last Observation Carried Forward	10
6.4. Patient Disposition	10
6.5. Important Protocol Deviations	10
6.6. Patient Characteristics	10
6.7. Historical Illness and Pre-existing Conditions	10
6.8. Concomitant Therapy	11
6.9. Treatment/Diary Compliance	11
6.10. Primary Outcome and Methodology	12
6.11. Efficacy Analyses	13
6.12. Health Outcomes/ Quality of Life Analyses	14
6.13. Safety Analyses	14
6.13.1. Extent of Exposure	14
6.13.2. Adverse Events	14
6.13.3. Vital Signs, Weight, and ECG Evaluation	15
6.13.4. Clinical Laboratory Evaluation	16
6.13.5. C-SSRS Analyses	16
6.13.6. Falls Analyses	16
6.14. Subgroup Analyses	16
6.15. Interim Analyses	17
7. Unblinding Plan	18
7.1. Site Level Unblinding	18
7.2. Sponsor/Trial Level Unblinding	18

8. References19

3. Revision History

SAP Version 1 was approved prior to the first patient visit.

SAP Version 2 was approved on Jun 02, 2017 prior to the final database lock.

Significant changes were made in the following sections:

- Section 5: Update the sample size based on the protocol Amendment.
- Section 6.1: Update the sample size based on the protocol Amendment; add the rationale for the assumption of treatment difference: 0.1.
- Section 6.4: Update the “patient discontinuation of study and study treatment” to “patient discontinuation of each study period”.
- Section 6.6: Add more patient disease characteristics to be summarized.
- Section 6.10: Remove the “*” and note for “*” in the weekly mean calculation table .
- Section 6.13.2: Update “AE leading to discontinuation of study drug and/or AE leading to discontinuation of study” to “AE leading to discontinuation”.
- Section 8: Update the references.
- Section 6.5: update major protocol viloations to important protocol deviations.

4. Study Objectives

4.1. Primary Objective

The primary objective of this study is to assess the noninferiority of duloxetine (40 to 60 mg/day) compared to pregabalin (300 to 600 mg/day) after 12 weeks of treatment in patients with diabetic peripheral neuropathic pain (DPNP), as measured by change from baseline in the weekly mean of the 24-hour average pain score, which will be measured using an 11-point numeric rating scale (NRS) in the daily patient diary.

4.2. Secondary Objectives

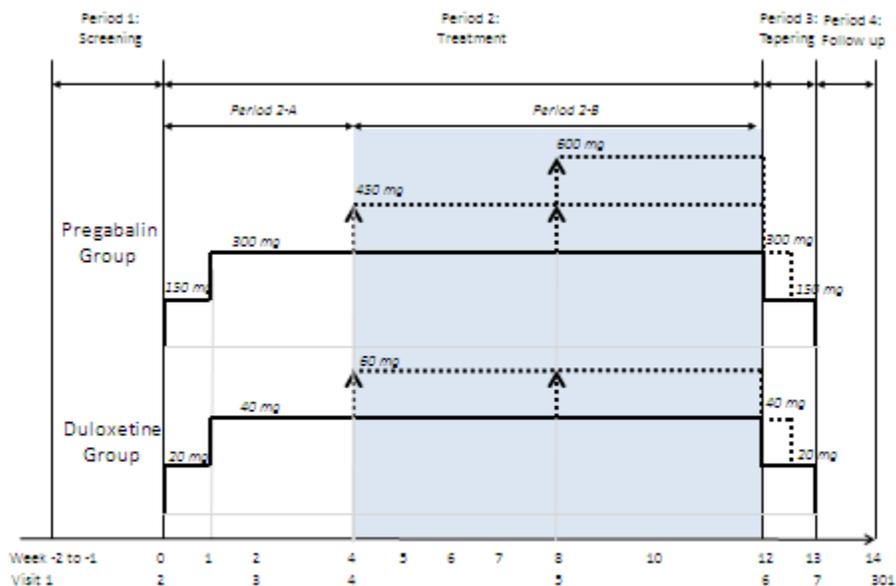
The secondary objectives of the study are as follows:

- To compare the efficacy of duloxetine (40 to 60 mg/day, orally) versus pregabalin (300 to 600 mg/day, orally) for the treatment of patients with DPNP as measured by:
 - Patient Global Impression of Improvement (PGI-I)
 - Brief Pain Inventory-Severity and Interference rating short form (BPI-SF)
 - Weekly mean of night pain and 24-hour worst daily pain scores measured using an 11-point NRS in the daily patient diary
 - Response to treatment, defined by a 30% and 50% reduction of the weekly mean of the 24-hour average pain score measured using an 11-point NRS in the daily patient diary
 - Neuropathic Pain Symptom Inventory (NPSI)
 - Clinical Global Impressions of Improvement (CGI-I)
 - EuroQol 5 Dimension (EQ-5D)
 - Beck Depression Inventory-II (BDI-II) Total score
- To evaluate the safety and tolerability of duloxetine compared with pregabalin for the treatment of patients with DPNP as measured by frequencies of treatment-emergent adverse events (TEAEs), including edema, the discontinuation rates due to adverse events (AEs), and clinical laboratory tests (including hemoglobin A1c [HbA1c] and glucose).

5. Study Design

Study F1J-JE-HMHA (1413N0841) is a post-marketing, Phase 4, multicenter, randomized, double-blind, parallel-group, flexible-dose, comparative study to assess the noninferiority of duloxetine (40 to 60 mg/day) compared with pregabalin (300 to 600 mg/day) for 12 weeks in approximately 286 adult outpatients with DPNP (143 patients per arm).

Figure HMHA.1 illustrates the study design, which includes a screening period (approximately 1 to 2 weeks), treatment period (12 weeks), tapering period (1 week), and follow-up period (1 week). The study periods are further described below.



Dosage is shown as mg/day. Duloxetine will be administered once daily (QD) and Pregabalin will be administered twice daily (BID).

Figure HMHA.1. Illustration of study design for Clinical Protocol F1J-JE-HMHA (1413N0841).

Period 1 - Screening (1 to 2 weeks): The screening period will consist of a minimum of 7 days and a maximum of 14 days. Patients will not be allowed to use any prohibited medications and therapies from Period 1. During this period, patients will be screened for eligibility. An informed consent form (ICF) approved by an institutional review board (IRB) will be signed by the patient. Informed consent must be obtained before any study procedures are performed. During screening procedures, no study drug will be administered.

Period 2 - Treatment (12 weeks): The treatment period will begin at Visit 2 (Day 0) and end at Visit 6 (Week 12). At the beginning of Visit 2 (Day 0), patients will be randomly assigned to duloxetine or pregabalin in a 1:1 ratio. Patients will take duloxetine QD orally after breakfast and

pregabalin BID orally as instructed by each respective package label . Duloxetine will be administered at 20 mg/day for 1 week and then 40 mg/day for 3 weeks. Pregabalin will be administered at 150 mg/day for 1 week and then 300 mg/day for 3 weeks.

At Visit 4 (Week 4) and at Visit 5 (Week 8), duloxetine and pregabalin doses may be increased in patients who do not achieve ≥ 30 % pain improvement in the BPI-SF average pain score compared with baseline (Visit 2). At either week, duloxetine may be increased to 60 mg/day and pregabalin may be increased to 450 mg/day. If pregabalin is increased to 450 mg/day at Visit 4 (Week 4), it may be further increased to 600 mg/day at Visit 5 (Week 8). Patients will not be allowed to decrease their dose once increased. If patients are unable to tolerate a dosage increase during Period 2, they should be discontinued from the study.

Period 3 - Tapering (1 week): Period 3 is a 1-week tapering period to minimize discontinuation-emergent AEs. Patients receiving a final dose of duloxetine at 60 mg/day during double-blind treatment will receive 40 mg/day for the first 3 days of the 1-week tapering period and then 20 mg/day for the last 4 days. Patients receiving a final dose of duloxetine at 40 mg/day during double-blind treatment will receive 20 mg/ day throughout the 1-week tapering period. Patients receiving a final dose of pregabalin at 600 mg/day or 450 mg/day during double-blind treatment will receive 300 mg/day for the first 3 days of the 1-week tapering period and 150 mg/day for the last 4 days. Patients receiving a final dose of pregabalin at 300 mg/day during double-blind treatment will receive 150 mg/day throughout the 1 week tapering period.

Period 4 - Follow Up (1 week): During the follow-up period, no study drug will be administered. The purpose of this period is to investigate AEs that occurred 1 week after discontinuation of the study drug with or without tapering.

6. A Priori Statistical Methods

6.1. Determination of Sample Size

Approximately 286 patients will be randomized in a 1:1 ratio to duloxetine or pregabalin respectively.

Sample size was calculated in order to have enough statistical power to confirm the non-inferiority of duloxetine to pregabalin based on the primary endpoint, the change from baseline to Week 12 in the weekly mean of the 24-hour average pain score, which will be evaluated using an 11-point NRS in the daily patient diary. Assuming that the treatment difference of the primary endpoint is 0.1 (i.e. duloxetine is superior to pregabalin by 0.1) and that the common standard deviation (SD) of the primary endpoint is 1.82 with a non-inferiority margin of 0.51, 141 patients per group (282, in total) would have a statistical power of 80% to confirm the noninferiority with a 1-sided significance level of 0.025.

The treatment difference could be assumed to be at least 0.1 in this study based on the results such as the double-blind randomized study to comparing duloxetine and pregabalin (the treatment difference [95% confidence interval (CI)]: 0.61 [0.33, 0.90]) (Bouhassira et al. 2014, Marchettini et al. 2016, Tesfaye et al. 2013) and the results of the meta-analysis comparing them indirectly (the treatment difference [95% credible interval]: 0.25 [-0.16, 0.67]) (Quilici et al. 2009) even though there are differences such as treatment periods among the studies.

The noninferiority margin was estimated based on a meta-analysis that applied the DerSimonian-Laird method. Utilizing a phase 3 trial of pregabalin in Japan, which was treated as an evaluation-test in either Japan or the US, this meta-analysis looked at the difference of variation in the average pain score between placebo and pregabalin after 12 weeks of treatment. It was estimated that the difference of the mean value and its 95% CI was 1.03 (0.69, 1.37). The non-inferiority margin for the current study was set using half of the difference of the mean value, 0.51 (that is, 1.03/2). The SD was assumed to be 1.82, based on the pooled analysis results of 1 pregabalin trial and 2 duloxetine trials conducted in Japan.

6.2. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly. Analyses will be conducted using SAS 9.2 (or later).

Efficacy analyses will be conducted on the full analysis set (FAS), unless otherwise stated. The FAS includes all data from all randomized patients receiving at least 1 dose of the study drug according to the treatment the patients were assigned. When mean change from baseline to endpoint is assessed, data will be included in the analysis only if there is a baseline and a corresponding postbaseline measure.

Safety analyses will be conducted on the safety analysis set. This set includes all randomized patients who received at least 1 dose of study drug. Safety analyses will be based on the treatment the patients actually received.

Analyses based on the per-protocol set (PPS) will be performed to examine the robustness of the primary efficacy analysis. The PPS will be defined as a subset of patients in FAS who did not have major protocol deviations.

All tests of hypotheses will be considered statistically significant if the 2-sided p-value is <0.05 , unless otherwise stated. No adjustments for multiple comparisons will be made.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the SAP and clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

Baseline value for a variable will be defined as the last non-missing value for this variable prior to or at randomization visit (Visit 2), unless otherwise specified.

The endpoint value for an efficacy variable is defined as the last non-missing post baseline value prior to or at Visit 6 (Week 12), unless otherwise stated.

The endpoint value for a safety variable is defined as the last non-missing post baseline value prior to or at Visit 7 (Week 13), unless otherwise stated.

In general, descriptive summary statistics will include:

- for categorical variables: number and percentage (with the percentage excluding the number missing in the denominator)
- for continuous variables: number, mean, median, standard deviation, minimum, and maximum.

Percentages will be reported to one decimal place; mean and median to one decimal place more than the raw data; standard deviation and standard error to two decimal places more than the raw data; minimum and maximum the same as the raw data.

Only one data lock is planned for this study, when all patients have completed all study procedures. No interim analyses are planned.

6.3. Handling of Dropouts or Missing Data

When the imputation for the missing data will be needed, the baseline observation carried forward (BOCF) and last observation carried forward (LOCF) methods will be used for the primary efficacy endpoint. And the LOCF method will be used for the others. The imputation will not be conducted unless otherwise stated.

6.3.1. Baseline Observation Carried Forward

A BOCF analysis will be performed on the primary variable. For patients discontinuing the study drug due to an adverse event (AE), death or lack of efficacy, the baseline observation will be carried forward to the corresponding primary endpoint evaluation. Otherwise, the last non-missing post baseline observation will be carried forward to the corresponding primary endpoint

for evaluation. Randomized patients without at least 1 post baseline observation will not be included for evaluation with the exception of patients discontinuing study treatment due to an AE, death or lack of efficacy.

6.3.2. Last Observation Carried Forward

A LOCF analysis will be performed on the primary and the other variables unless otherwise stated. Regardless the patients completed the study or discontinued the study treatment due to any reason, the last non-missing post baseline observation will be carried forward to the corresponding endpoint for evaluation. Randomized patients without at least one post-baseline observation will not be included for evaluation.

6.4. Patient Disposition

Reasons for study and study treatment discontinuation will be summarized by treatment group and period including treatment period, tapering period and follow-up period. The significance of the differences in percentages of each reason for discontinuation between the duloxetine and pregabalin treatments groups will be assessed using the Fisher's exact test.

By-patient listing of patient discontinuation of each study period will be presented for all randomized patients.

6.5. Important Protocol Deviations

The number and percentage of patients with important protocol deviations will be summarized and listed for all randomized patients.

6.6. Patient Characteristics

Patient demographics (age, gender, race, height, and weight) and patient disease characteristics (types of diabetic mellitus, duration of diabetes, duration of diabetic neuropathy, duration of diabetic neuropathy pain, alcohol consumption, and baseline HbA1c) will be summarized for the FAS population, as well as the baseline pain severity measurements (weekly mean of 24-hour average pain score, weekly mean of night pain score, weekly mean of 24-hour worst pain score, and BPI-SF score). In addition, baseline assessment for mood and general illness (PGI-Severity, BDI-II, NPSI, and CGI-Severity) will be summarized for the FAS population. For each of the measures mentioned above, the overall treatment group differences will be examined using the Analysis of Variance (ANOVA) model, with the terms of treatment for the continuous variables, and the Fisher's exact test for the categorical variables.

6.7. Historical Illness and Pre-existing Conditions

Significant historical illnesses and pre-existing conditions will be coded from the actual term using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

Pre-existing conditions are defined as those conditions recorded on the Pre-existing Conditions and AEs electronic case report forms (eCRF) page with a start date prior to the date of informed consent, and no end date (i.e. the event is ongoing) or an end date after the date of informed consent. If a pre-existing condition worsens in severity on or after the date of informed consent,

it will be considered an AE from the date of worsening onwards. Patients will only be counted once, regardless of how many conditions are included under the same System Organ Class (SOC) and Preferred Term.

The number and percentage of patients with significant historical illness will be summarized by treatment group by MedDRA Preferred Term based on the FAS population. In addition, the number and percentage of patients with pre-existing conditions will be summarized similarly.

By-patient listings of historical illnesses and pre-existing conditions will be provided.

6.8. Concomitant Therapy

Medications will be coded according to the World Health Organization (WHO) dictionary. Previous medications are those medications that started and stopped before the first day of the study treatment. Concomitant medications are those medications used during the study.

The number and percentage of patients with previous medications will be summarized by Anatomical Therapeutic Chemical (ATC) class (level 4) and WhoDrug preferred term and by treatment group.

The number and percentage of patients receiving concomitant medications other than analgesics and the number and percentage of patients receiving analgesics concomitant medications will be summarized by ATC class (level 4) and WhoDrug preferred term and by treatment group respectively. The significance of differences between the treatment groups will be assessed via the Fisher's exact test.

By-patient listings of previous medications and concomitant medications will be provided.

6.9. Treatment/Diary Compliance

Treatment compliance will be calculated based on the number of capsules taken (calculated from the number of capsules dispensed and returned) and the number of days between visits as a percentage of the number of capsules prescribed for a period of that length. Patients will be considered compliant for a particular visit if 80% to 120% of the prescribed capsules were taken. Overall treatment compliance will be defined as being compliant at all non-missing visits. The numbers and percentages of patients with treatment compliance or non-compliance with compliance level (Never (0%), Significantly less than prescribed (<80%), and More frequently than prescribed (>120%)) will be summarized by visits and overall by treatment group, and the treatment group differences will be assessed via the Fisher's exact test.

A patient will be considered to be compliant with the diary at a certain visit if the patient completed at least 80% of the diaries over the total days since the last visit. A patient will be considered to be compliant overall with the diary if the patient is compliant with the diary at each visit in the study period from Visit 2 through Visit 6. Diary compliance percentages will be summarized descriptively for all visits by treatment group. The numbers and percentages of patients with diary compliance will be summarized by visits and overall by treatment group, and the treatment group differences will be assessed via the Fisher's exact test.

By-patient listings of treatment compliance and diary compliance will be provided.

6.10. Primary Outcome and Methodology

The primary efficacy variable is the change from baseline in the weekly mean of the 24-hour average pain score measured using an 11-point NRS in the daily patient diary. The weekly mean of the 24-hour average pain score for each week will be the mean score for the following duration:

Week	Duration used for the calculation of weekly mean
Baseline	Day -6 to Day 0
1	Day 2 to 7
2	Day 8 to 14
3	Day 15 to 21
4	Day 22 to 28
5	Day 29 to 35
6	Day 36 to 42
7	Day 43 to 49
8	Day 50 to 56
9	Day 57 to 63
10	Day 64 to 70
11	Day 71 to 77
12	Day 78 to 84

A mixed-model repeated measures (MMRM) analysis will be the primary analytical technique to assess mean change in efficacy measures. The MMRM model will include the random effect of patient and fixed categorical effects of treatment, duration of DPNP (<2 years, ≥2years), week, and treatment-by-week interaction, as well as the continuous fixed covariates of baseline value. An unstructured covariance structure will be used to model the within-patient errors. A Kenward-Rogers correction (Kenward and Roger 1997) will be used to estimate denominator degrees of freedom.

The difference in LS mean between treatments (duloxetine minus pregabalin) at Week 12, along with its 2-sided 95% CI, will be calculated, based on the model. If the upper bound of the 95% CI does not exceed 0.51, it will be concluded that duloxetine is not inferior to pregabalin.

If the model with unstructured covariance structure fails to converge, the sandwich estimator be used to estimate the standard errors of the fixed effects parameters and the model will be fit using covariance structures of the following order until convergence is met:

- heterogeneous toeplitz type = toeph
- heterogeneous autoregressive (1st order) type = arh(1)
- heterogeneous compound symmetric type = cs(h)
- toeplitz type = toep
- autoregressive (1st order) type = ar(1)
- compound symmetric type = cs

If the sandwich estimator is used, the Kenward-Roger approximation for denominator degrees of freedom cannot be used; instead, the denominator degrees of freedom will be partitioned into between-subject and within-subject portions (denoted by DDFM= BETWITHIN in the MODEL statement).

An analysis of covariance (ANCOVA) model will be used to analyze the change from baseline to Week 12 in the weekly mean of the 24-hour average pain score measured using an 11-point NRS in the daily patient diary. The model will contain the main effects of treatment and duration of DPNP (<2 years, ≥2years) as well as the continuous fixed covariates of baseline value. The LS mean will be used for the statistical comparisons using ANCOVA.

For the imputation of the missing values, the following 2 methods: BOCF and LOCF will be used. Both analyses will be performed as a secondary analysis to examine the robustness of the primary analysis result.

6.11. Efficacy Analyses

The secondary efficacy objectives will be addressed by conducting MMRM analyses (as described in [Section 6.10](#), but without the baseline score in the model for CGI-I and PGI-I, and week will be replaced by visit except for items from diary) to compare treatment differences for the following variables:

- From the BPI-SF, each of the 4 questions assessing the severity of worst pain, least pain, and average pain in the past 24 hours, and the pain right now
- From the BPI-SF, each of the 7 questions assessing the interference of pain with activities and the mean of the seven questions
- Weekly mean of night pain and worst pain scores measured using 11-point NRS in the daily patient diary
- BDI-II total score
- CGI-I and PGI-I

For the NPSI questionnaire, the total score and each of the 5 subscores: burning spontaneous pain, pressing spontaneous pain, paroxysmal pain, evoked pain, and paresthesias/dysesthesias will be addressed by ANCOVA analysis (as described in [Section 6.10](#)) to compare treatment differences. Missing data will be imputed using LOCF method.

Further secondary objectives will be addressed by comparing treatment groups with respect to the proportions of patients achieving each of the following at Visit 6 (Week 12) using Fisher's exact test. In this analysis, missing data will be imputed using LOCF method:

- A $\geq 30\%$ reduction on the weekly mean of the 24-hour average pain score measured using an 11-point NRS in the daily patient diary
- A $\geq 50\%$ reduction on the weekly mean of the 24-hour average pain score measured using an 11-point NRS in the daily patient diary

6.12. Health Outcomes/ Quality of Life Analyses

The European Quality of Life - 5 dimension (EQ-5D) questionnaire consists of five items: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In addition, a Quality of Life "thermometer" visual analog scale (VAS) is presented that is rated from 0 to 100. For each item patients will choose one of the three options that best described the status. The three options reflecting increasing degrees of difficulty are coded as 1, 2, and 3. Scores from the five items form a five-digit code that describes the respondent's health state. This five-digit code will be then converted to a weighted index (called EQ-5D index) using Japanese population values. The change from baseline to endpoint in the EQ-5D index and VAS score will be analyzed by the ANCOVA model (as described in [Section 6.10](#)). Missing data will be imputed with LOCF method.

6.13. Safety Analyses

Safety will be assessed by summarizing and analyzing extent of exposure, AEs (SAEs, TEAEs, and adverse drug reactions), discontinuations due to AEs, Fall Questionnaire, laboratory measurements, vital signs, weight, and electrocardiogram (ECG) results. In addition, suicide risk and suicide-related events (behavior and/or ideation) as assessed by the C-SSRS.

6.13.1. Extent of Exposure

Treatment exposure is defined as the time from when the patient is randomized at Visit 2 and receives study drug until the last treatment dose date.

Treatment exposure will be listed and further summarized by treatment arm based on the safety analysis set. Duration of exposure will be categorized into the following groups: >0 - 14 days, >14 - 28 days, >28 - 42 days, >42 - 56 days, >56 - 84 days, and >84 days. These categories will be summarized as frequency by treatment group. Summary statistics will include mean per patient exposure in days, SD, median, minimum, and maximum.

In addition, a frequency table of doses at visit 4 and visit 5 will be provided.

6.13.2. Adverse Events

An adverse event is any untoward medical event associated with the use of a drug in humans, whether or not it is considered related to a drug. Adverse events will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by treatment group. TEAEs for treatment period will be defined as events that are newly reported or reported

to worsen in severity after the initiation of study drug through the treatment period. TEAEs for tapering period will be defined as events that are newly reported or reported to worsen in severity during the tapering period. Similarly, TEAEs for follow-up period will be defined as events that are newly reported or reported to worsen in severity during the follow-up period. The incidence of patients with at least one TEAE and the incidence of TEAEs by MedDRA preferred term and system organ class will be presented by treatment group. Fisher's exact test will be used for treatment comparison. These analyses will be summarized by treatment period, tapering period and follow-up period separately, and summarized for combined periods (treatment + tapering + follow-up). All the other analyses below will be summarized for combined periods only.

Treatment-Emergent Adverse Drug Reactions (ADR) will be also by summarized using MedDRA Preferred Term by treatment group. Here, Treatment-Emergent ADR means that TEAEs indicated by the investigator on the Case Report Form (CRF) to be possibly related to the study drug. Similarly, summaries of serious adverse event (SAE), AE leading to discontinuation will be provided separately.

The incidence of patients with TEAEs by maximum severity will be summarized by treatment group using MedDRA Preferred Term nested within System Organ Class.

An overview of AEs will be provided. This summary will include the number and percentage of patients who experienced a TEAE, death, SAE, ADRs, AE leading to discontinuation.

By-patient listings of TEAEs, and SAEs (including death) including the same event on several occasions will be presented. The listings will include both preferred term and the original term used by the investigators.

6.13.3. Vital Signs, Weight, and ECG Evaluation

Change from baseline to Visit 7 in vital signs, body weight will be analyzed by the ANCOVA model with treatment as the fixed effect and baseline value as a covariate for between-group differences. Missing data will be imputed by LOCF method.

The numbers and percentages of patients with treatment-emergent abnormal, high, or low vital signs at any time during treatment or tapering period will be summarized and compared between treatment groups using Fisher's exact test.

A treatment-emergent abnormal result is defined as a change from normal at baseline to abnormal at any time during the treatment or tapering period. A treatment-emergent high result is defined as a change from a value less than or equal to the high limit at baseline to a value greater than the high limit at any time during the treatment or tapering period. A treatment-emergent low result is defined as a change from a value greater than or equal to the low limit at baseline to a value less than the low limit at any time during the treatment or tapering period.

By-patient listings of vital signs, body weight and ECG will be presented for all randomized patients.

6.13.4. Clinical Laboratory Evaluation

Change from baseline to Visit 7 in each of the laboratory tests (including the groups of hematology, clinical chemistry (including HbA1c and glucose), urinalysis) will be analyzed by the ANCOVA model with treatment as the fixed effect and baseline value as a covariate for between-group differences. Missing data will be imputed by LOCF method.

The numbers and percentages of patients with treatment-emergent abnormal, high, or low laboratory results at any time during treatment or tapering period will be summarized and compared between treatment groups using Fisher's exact test.

A treatment-emergent abnormal result is defined as a change from normal at baseline to abnormal at any time during the treatment or tapering period. A treatment-emergent high result is defined as a change from a value less than or equal to the high limit at baseline to a value greater than the high limit at any time during the treatment or tapering period. A treatment-emergent low result is defined as a change from a value greater than or equal to the low limit at baseline to a value less than the low limit at any time during the treatment or tapering period.

A lab listing for all randomized patients will be provided, including the actual measurement, abnormal result, and reference low or high limits.

6.13.5. C-SSRS Analyses

Suicide-related thoughts and behaviors based on the Columbia-Suicide Severity Rating Scale (C-SSRS) will be listed and summarized by treatment group. In particular, for each of the following suicide-related events, the number and percent of patients with the event will be enumerated by treatment: completed suicide, nonfatal suicide attempt, interrupted attempt, aborted attempt, preparatory acts or behavior, active suicidal ideation with specific plan and intent, active suicidal ideation with some intent to act without specific plan, active suicidal ideation with any methods (not plan) without intent to act, nonspecific active suicidal thoughts, and wish to be dead.

6.13.6. Falls Analyses

Numbers and percentages of patients with any falls will be summarized by treatment group and visit.

By-patient listing of fall questionnaire will be presented for the all randomized patients.

6.14. Subgroup Analyses

Subgroup analyses may be conducted on primary efficacy outcomes. Depending on the number of patients per strata, analyses may be conducted by the following subgroups :

- DPNP duration (<2 years, ≥2years)
- Baseline weekly mean of the 24-hour average pain score (<6, ≥6)
- Baseline HbA1c (<6.5%, ≥6.5%)

Subgroup analyses will be implemented using the repeated measures approach as described for either continuous or categorical variables, with the addition of strata, strata-by-week, strata-by-treatment, and strata-by- treatment -by-week interactions to the model.

6.15. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the appropriate Lilly regulatory scientist will be consulted to determine whether it is necessary to amend the protocol.

7. Unblinding Plan

The purpose of this unblinding plan is to maintain the scientific integrity of the study. The following actions/procedures will be put in place prior to any unblinding of the study data.

7.1. Site Level Unblinding

The procedure for site personnel to unblind an individual subject's treatment assignment for emergency is described in the protocol.

The site monitor is responsible for verifying compliance with the blinding procedures at the investigator site and verifying that access to the subjects' treatment assignments has remained restricted from the investigator and site personnel in direct contact with subjects.

The investigator and site personnel are instructed to make every attempt to contact Lilly personnel when a subject's treatment assignment is unblinded at the site. The affiliate personnel document the unblinding records and inform the designated study team member, the Clinical Development Associate (CDA), who documents the overall unblinding records for the entire study. The documentation is filed in the study files. A final Study Unblinding Summary will be prepared at the end of the study (at the study closeout).

7.2. Sponsor/Trial Level Unblinding

The following personnel with direct site contact or personnel responsible for data entry and data validation will remain blinded until datalock for the final data analysis is authorized in order to protect the scientific integrity of the study conduct and prevent introduction of bias:

- Clinical Research Associate
- CDA
- Data Management Associate (Systems Analyst)
- Project Statistician
- Clinical Research Physician
- Clinical Research Scientist
- Scientific Communication Associate

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Leo Document ID = 5ab25318-c522-4779-9398-bd2b05751bc3

Approver: PPD

Approval Date & Time: 02-Jun-2017 09:30:59 GMT

Signature meaning: Approved