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: 17-Apr-2015

1. Protocol F1J-JE-HMHA (1413N0841) (b) 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

Duloxetine hydrochloride (LY248686)

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.
Kobe, Japan

Shionogi & Co., Ltd.
Osaka, Japan

Protocol Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 17-Apr-2015 GMT

2. Synopsis

Study Rationale

Duloxetine was submitted to Pharmaceuticals and Medical Devices Agency (PMDA) for the indication of diabetic peripheral neuropathic pain (DPNP) in Japan, and received approval on 22 February 2012. As part of the new drug application (NDA), 2 double-blind clinical studies were conducted in Japan (Phase 2 F1J-JE-HMFE [0512N0821] and Phase 3 F1J-JE-HMFX [0715N0831]). Duloxetine efficacy was shown in this Phase 3 study (Yasuda et al. 2011); however, during the NDA review period, PMDA judged that an additional clinical trial was necessary to confirm duloxetine efficacy. Thus, PMDA requested that Shionogi Co., Ltd. conduct a post-marketing clinical trial to confirm efficacy. Shionogi is an alliance partner of Lilly and holder of the NDA for Cymbalta in Japan. Following discussion of the study design with PMDA and Shionogi, it was agreed that Lilly Japan would conduct 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 DPNP (Study F1J-JE-HMHA [1413N0841]).

Clinical Protocol Synopsis: Study F1J-JE-HMHA (1413N0841)

Name of Study Drug: Duloxetine hydrochloride (LY248686)

Title of Study: 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

Number of Planned Patients/Subjects: Enrolled/Randomized: 410 (205 per arm)	**Phase of Development:** 4

Length of Study: approximately 2.5 years
Estimated first patient visit: 01 October 2014 Estimated last patient visit: 01 February 2017

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.

Secondary Objectives:

Secondary objectives of this study are:

- To compare the efficacy of duloxetine (40 to 60 mg/day) versus pregabalin (300 to 600 mg/day) 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 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 Impression 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).

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 adult outpatients with DPNP. The study design includes a screening period (approximately 1 to 2 weeks), treatment period (12 weeks), tapering period (1 week), and follow-up period (1 week) as described below:

- **Period 1 - Screening:** The screening period will consist of a minimum of 7 days and a maximum of 14 days. During the screening period, no study drug will be administered.
- **Period 2 - Treatment:** 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. 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 once daily (QD) 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) in patients who still do not achieve ≥30 % pain improvement in the BPI-SF average-pain score compared with baseline (Visit 2).

- **Period 3 - Tapering:** 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 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:** During the 1-week 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.

Diagnosis and Main Criteria for Inclusion and Exclusions: Eligible patients are male or female outpatients ≥20 and <80 years of age that present with pain due to bilateral, peripheral neuropathy as determined by the simplified screening criteria from the Working Group for Diabetic Neuropathy on 18 January 2002, partially modified version. In addition, patients must have: (1) HbA1c ≤9.4% (National Glycohemoglobin Standardization Program [NGSP]) at Visit 1; (2) a HbA1c that has been measured 42 to 70 days prior to Visit 1, and the range of variation in the values measured, thereafter, is within ±1.0% of the value measured at Visit 1; and (3) a score of at least 4 on the mean of the 24-hour average pain score measured using the 11-point NRS in the daily patient diary (should be calculated from records 7 days immediately prior to Visit 2). Key exclusion criteria include the following: (1) glycemic control has been poor within 70 days immediately prior to Visit 1; (2) past history of psychiatric diseases, such as depression, anxiety disorder, eating disorder, etc., that required drug therapy in the past 1 year, or current complications of these diseases or any history of manic psychosis or bipolar disorder; (3) major depressive disorder (MDD); (4) complications of diseases that are considered to affect the assessment of diabetic peripheral neuropathic pain; and (5) neuropathic pain suspected to be caused by alcohol.

Study Drug, Dosage, and Mode of Administration: Duloxetine 20, 40, or 60 mg/day, given once daily (QD) as 20 mg capsules orally.

Reference Therapy, Dose, and Mode of Administration: Pregabalin 150, 300, 450, or 600 mg/day, given twice daily (BID) as 25 or 150 mg capsules orally

Planned Duration of Treatment: 13 weeks for a single patient

- Treatment period: 12 weeks
- Tapering period: 1 week

Criteria for Evaluation:

Efficacy:

- The 24-hour average pain, the night pain, and the 24-hour worst pain scores measured using an 11-point NRS in the daily patient diary
- Patient's Global Impressions of Improvement (PGI-I)
- Brief Pain Inventory (BPI)–Severity and Interference (short form) (BPI-SF)
- Neuropathic Pain Symptom Inventory (NPSI)
- Beck Depression Inventory-II (BDI-II)
- Clinical Global Impressions of Improvement (CGI-I)

Safety:

- Spontaneously reported AE (including edema), serious adverse events (SAEs), electrocardiograms (ECGs), vital signs, body weight, and laboratory measurements (clinical chemistry, hematology, urinalysis)
- Columbia Suicide Severity Rating Scale (C-SSRS) and self-harm follow-up form
- Fall Questionnaire

Health Outcomes:

- EuroQol 5 Dimension (EQ-5D)

Other Measures (Baseline Only):

- Patient's Global Impressions of Severity
- Clinical Global Impressions of Severity
- Mini-International Neuropsychiatric Interview (MINI): MDD module only

Statistical Methods:

General Considerations: Efficacy analyses will be conducted on the full analysis set (FAS). 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. 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.

Efficacy/Health Outcome: The primary efficacy variable is the change from baseline in the weekly mean of the 24-hour average pain score measured using the 11-point NRS in the daily patient diary. A mixed-model repeated measures (MMRM) analysis will be the primary analytical technique to assess mean change in the primary 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 will be used to estimate denominator degrees of freedom. The difference in least squares (LS) mean between treatments (duloxetine minus pregabalin) at Week 12 along with its 2-sided 95% confidence interval (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. An analysis of covariance (ANCOVA) model will be also used to analyze the change from baseline to Week 12 in the primary efficacy variable. 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 last observation carried forward (LOCF) and baseline observation carried forward (BOCF) methods will be used.

Safety: Safety will be assessed by summarizing and analyzing AEs (SAEs, TEAEs, adverse drug reactions), discontinuation (rates and reasons), Fall Questionnaire, laboratory measurements, vital signs, weight, and ECGs. In addition, suicide risk and suicide-related events (behavior and/or ideation) as assessed by the C-SSRS.

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4. Abbreviations and Definitions

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
BDI-II	Beck Depression Inventory-II
BID	twice daily
blinding	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not. A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BOCF	baseline observation carried forward
BPI-SF	Brief Pain Inventory-Short Form
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.

Term	Definition
compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
CrCL	creatinine clearance
C-SSRS	Columbia Suicide Severity Rating Scale
DPNP	diabetic peripheral neuropathic pain
DSM-IV-TR	*Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision
ECG	electrocardiogram
eCRF	electronic case report form
ED	early discontinuation
efficacy	Efficacy is the ability of a treatment to achieve a beneficial intended result under controlled conditions.
end of trial (study)	End of trial is the date of the last visit or last scheduled procedure shown in the Study Schedule for the last patient.
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ePRO	electronic patient-reported outcomes
EQ-5D	EuroQol 5 Dimension
FAS	full analysis set
FDA	Food and Drug Administration
FOIA	Freedom of Information Act
GCP	good clinical practice
HbA1c	hemoglobin A1c
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th revision
ICF	informed consent form
ICH	International Conference on Harmonisation

Term	Definition
Informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
IRB	institutional review board: A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical study are protected.
IWRS	interactive web-response system
JSPC	Japan Society of Pain Clinicians
legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient, to the patient's participation in the clinical study.
LOCF	last observation carried forward
LS mean	Least square mean
MAO	Monoamine oxidase
MDD	major depressive disorder
MHLW	Ministry of Health Labor and Welfare
MHLW-PAB	Ministry of Health Labor and Welfare-Pharmaceutical Affairs Bureau
MINI	Mini-International Neuropsychiatric Interview
MMRM	Mixed-model repeated measures
NDA	new drug application
NGSP	National Glycohemoglobin Standardization Program
NIMH	National Institutes of Mental Health
NPSI	Neuropathic Pain Symptom Inventory
NRS	numeric rating scale
patient	A study participant who has the disease or condition for which the study drug is targeted.

Term	Definition
PGI-I	Patient Global Impressions of Improvement
PGI-S	Patient Global Impression of Severity
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	per-protocol set: The set of data generated by the subset of patients who sufficiently complied with the protocol to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model.
QD	once daily
randomize	The process of assigning patients to an experimental group on a random basis.
re-screen	To screen a patient who was previously declared a screen failure for the same study.
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. In this study, screening involves tests (for example, psychological tests and blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
SD	standard deviation
SNRI	serotonin and norepinephrine reuptake inhibitor
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
subject	An individual who is or becomes a participant in clinical research, either as a recipient of the study drug(s) or as a control. A subject may be either a healthy human or a patient.
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
TPO	third-party organization
ULN	upper limit of normal
US	United States
VAS	visual analog scale

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

5. Introduction

Recently, the number of patients with diabetes in Japan has increased most likely due to life-style changes. Approximately 9.5 million people in Japan have diabetes, and even more are estimated to have either diabetes or preliminary diabetes (20.5 million). This is approximately one-seventh of adults in Japan (MHLW 2013). Three major complications of diabetes are diabetic neuropathy, diabetic retinopathy, and diabetic nephropathy. Among these, diabetic neuropathy is the most common, and approximately 15.6 % of diabetic patients have diabetic neuropathy (MHLW 2002). Moreover, diabetic neuropathy causes a painful physical symptom known as diabetic peripheral neuropathic pain (DPNP). With the recent increase in diabetes in Japan, the number of diabetic patients with diabetic neuropathy and DPNP is estimated to increase.

The first and most important treatment for all DPNP patients is maintaining glucose concentrations within the normal range. Tight glycemic control can prevent progression of diabetic neuropathy (Amthor et al. 1994) and multiple studies have shown that improving glycemic control can reduce pain in DPNP patients (Archer et al. 1983, Boulton et al. 1982, Oyibo et al. 2002). However, DPNP commonly occurs even in patients with good glycemic control (Sorensen et al. 2002), and pharmacologic treatments directed at pain are often necessary to manage DPNP.

Historically, epalrestat and mexiletine hydrochloride have been widely used in Japan for the treatment of DPNP. Both epalrestat and mexiletine are listed as therapeutic options for DPNP in the Japanese guideline for neuropathic pain management (JSPC 2011). Other medications listed in the treatment guideline include antidepressants, anticonvulsants, and sustained-release oxycodone. Tricyclic antidepressants, certain anticonvulsants, and opioid analgesics appear to also provide temporary relief to patients with DPNP, but use of these medications is limited by side effects (McQuay et al. 1996).

Recently, duloxetine and pregabalin have received approval by the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan for management of DPNP. Duloxetine is a serotonin and norepinephrine reuptake inhibitor (SNRI), and is thought to reduce the perception of pain by increasing the activity of descending pain pathways that dampen pain signals that arise from the periphery and are relayed through the spinal cord dorsal horn (Perahia et al. 2006). Duloxetine is indicated for the treatment of multiple diseases in overseas countries including major depressive disorder (MDD), generalized anxiety disorder, fibromyalgia, DPNP, and pain from osteoarthritis and chronic low back pain (Cymbalta package insert [PI]). In Japan, duloxetine is indicated for Depression/Depressive state and DPNP (Cymbalta PI), and used as a first-line medication for DPNP. Pregabalin is an anticonvulsant thought to reduce pain by binding to alpha2-delta subunits of presynaptic neuronal calcium channels, and reducing the release of excitatory

neurotransmitters involved in pain perception. Overseas, in addition to DPNP, pregabalin is indicated for the management of post-herpetic neuralgia, fibromyalgia, generalized anxiety disorder, and as an adjunct therapy for epilepsy (Lyrica PI). In Japan, pregabalin is indicated for neuropathic pain and pain associated with fibromyalgia.

Duloxetine was submitted to the PMDA in Japan for the indication of DPNP, and received approval on 22 February 2012. As part of the new drug application (NDA), 2 double-blind clinical studies were conducted in Japan (Phase 2 F1J-JE-HMFE [0512N0821] and Phase 3 F1J-JE-HMFX [0715N0831]). Duloxetine efficacy was shown in this Phase 3 study (Yasuda et al. 2011); however, during the NDA review period, PMDA judged that an additional clinical trial was necessary to confirm duloxetine efficacy. Thus, PMDA requested that Shionogi Co., Ltd. conduct a post-marketing clinical trial to confirm duloxetine efficacy (PMDA 2012). Shionogi is an alliance partner of Lilly and holder of the NDA for duloxetine (Cymbalta PI) in Japan. Following discussion of the study design with PMDA and Shionogi, it was agreed that Lilly Japan would conduct 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 DPNP (Study F1J-JE-HMHA [1413N0841]). The comparison between duloxetine and pregabalin is supported by the fact that both duloxetine and pregabalin are listed as first-line treatments in the international treatment guidelines for DPNP (NICE 2013) and in Japanese guideline (JSPC 2011), and that both have proven efficacy for the treatment of DPNP (O'Connor et al. 2009).

The primary objective of Study F1J-JE-HMHA (1413N0841) is to assess the non-inferiority of duloxetine (40 to 60 mg/day) given orally for 12 weeks compared with pregabalin (300 to 600 mg/day) given orally for 12 weeks in the treatment of patients with DPNP, as measured by change from baseline in the weekly mean of the 24-hour average pain score, which will be evaluated using an 11-point numeric rating scale (NRS) in the daily patient diary.

More detailed information about the known and expected benefits and risks of duloxetine hydrochloride may be found in the Cymbalta PI.

6. Objectives

6.1. 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 DPNP, as measured by change from baseline in the weekly mean of the 24-hour average pain score, which will be measured using an11-point NRS in the daily patient diary.

6.2. Secondary Objectives

Secondary objectives of this study are:

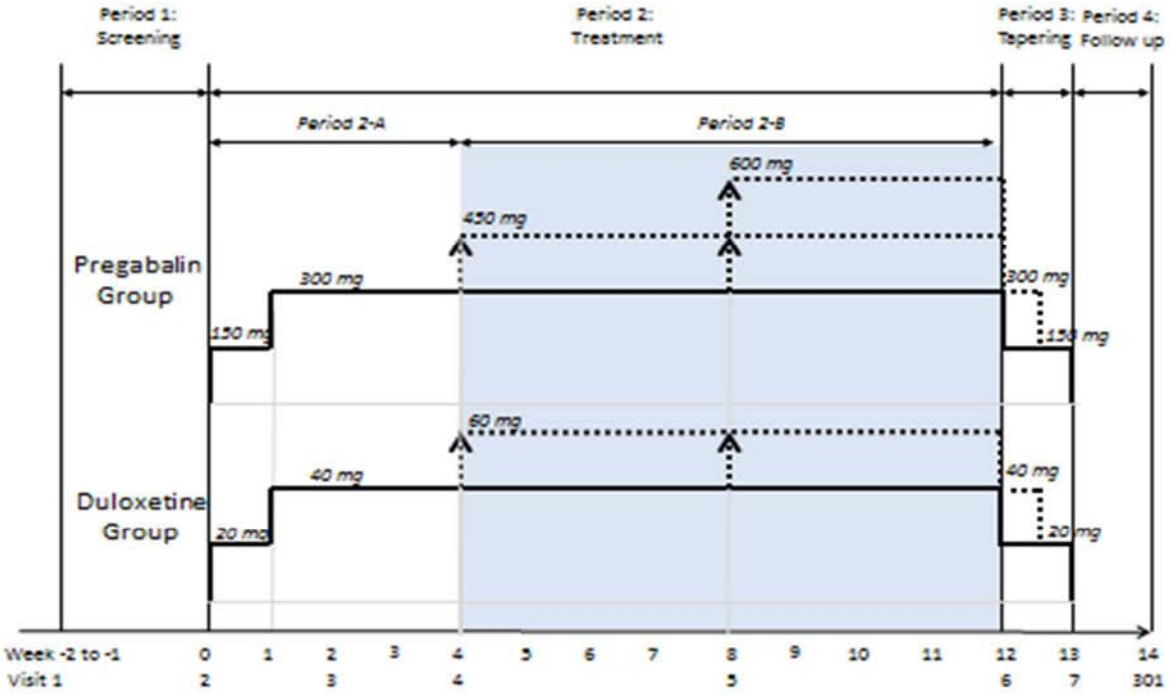
- To compare the efficacy of duloxetine (40 to 60 mg/day, orally) versus pregabalin (300 to 600 mg/day, orally) for the treatment of patients with DPNP as measured by:
    - Patient Global Impression of Improvement (PGI-I)
    - Brief Pain Inventory–Severity and Interference rating short form (BPI-SF)
    - 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).

7. Investigational Plan

7.1. Summary of 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 410 adult outpatients with DPNP (205 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 (Attachment 1). 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 (See Section 9.5). 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). See Section 9 for additional dosing details.

Based on clinical judgment and on individual patient tolerability, investigators may decide to keep patients, who don't achieve ≥30 % pain improvement, on the original dose (dose escalation is not mandatory). However, efficacy is not expected at lower doses for patients who will not receive dosage increases. From an ethical standpoint, these patients will be considered to discontinue the study in order to select another therapy option following tapering.

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. See Section 9.5.1 for additional details, including dose tapering for patients who discontinue early.

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.

7.2. Discussion of Design and Control

Pregabalin was chosen as a comparator in this study because it is used as a standard of care for DPNP in Japan as well as duloxetine (JSPC 2011).

The doses and dosage regimens chosen in this study are based on the current licensed dosages of study drugs, used as monotherapy, in Japan. 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 QD 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).

Based on clinical judgment and on individual patient tolerability, investigators may decide to keep patients, who don't achieve ≥30 % pain improvement, on the original dose (dose escalation is not mandatory). However, efficacy is not expected at lower doses for patients who will not receive dosage increases. From an ethical standpoint, these patients will be considered to discontinue the study in order to select another therapy option following tapering.

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.

The treatment period chosen for Period 2 is 12 weeks because previous Phase 3 trials of duloxetine and pregabalin in Japan were 12 weeks and 13 weeks, respectively. Although a treatment period of 13 weeks was used in a Phase 3 study of pregabalin in Japan, 12 weeks of treatment with pregabalin was chosen in the current study based on the following (Satoh et al. 2011):

- Improvements in the weekly mean of the pain scores in the daily pain diary were observed as early as 1 week after beginning treatment with pregabalin, and these improvements were sustained throughout the study period.
- In the 600-mg pregabalin group, change in pain scores appeared to reach a plateau at 4 weeks relative to the start of treatment.
- In the 300-mg pregabalin group, pregabalin treatment for 12 weeks showed almost the same efficacy as 13 weeks of treatment.

In addition, a foreign double-blind, placebo-controlled study of pregabalin showed that efficacy was achieved after 12 weeks of treatment including 1 week of titration (Tölle et al. 2008). These studies suggest that a 12-week treatment period is long enough to achieve efficacy with pregabalin.

Withdrawal symptoms are common with duloxetine, especially if discontinuation is abrupt, and have also been reported with pregabalin. Therefore, all patients will receive a tapered dose reduction over 1 week (Period 3). Other discontinued patients should also receive tapered study drug, whenever possible.

A randomized, double-blind study has been chosen in order to reduce bias in the collection of data. The study population has been chosen based on current use of the study drugs in clinical practice.

8. Study Population

Entered patients who meet the eligibility criteria at Visit 1 will proceed to Visit 2. At Visit 2, patients who continue to meet the applicable eligibility criteria will be randomized into double-blind treatment. Individuals who do not meet the criteria for participation in this study (screen failures) may be re-screened.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

8.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria at Visit 1, and Visit 2, where indicated:

[1] Male or female outpatients ≥20 and <80 years of age at the time of obtaining informed consent

[2] Present with pain due to bilateral, peripheral neuropathy (see disease diagnostic criteria below)

[3] Have a level of understanding sufficient to provide written informed consent and to communicate with the investigator and site personnel

[4] Have HbA1c ≤9.4% (National Glycohemoglobin Standardization Program [NGSP]) at Visit 1

[5] Have HbA1c that has been measured 42 to 70 days prior to Visit 1, and the range of variation in the values measured, thereafter, is within ±1.0% of the value measured at Visit 1

[6] A score of at least 4 on the mean of the 24-hour average pain score measured using 11-point NRS in the daily patient diary (should be calculated from records 7 days immediately prior to Visit 2)

[7] Have made complete daily patient diary entries 80% or more of the time from Visit 1 to Visit 2

8.1.1. Disease Diagnostic Criteria

For the purposes of this study, patients with DPNP are defined by:

- The presence of pain due to bilateral, peripheral neuropathy, caused by type I or type II diabetes mellitus, which has manifested for at least 6 months, and is assessable in the feet, legs, or hands, as determined by the following symptoms:
    - Aching pain (including tingling pain, and strangling, punching, hauling, or wringing pain)
    - Burning pain
    - Smarting pain (including pricking pain)
    - Pinging and running pain (including keen, stabbing, and electric shock-like pain, or paroxysmal pain sustaining for several seconds to several minutes)
    - Pain induced by stimulation that usually causes no pain (allodynia)

- A diagnosis of diabetic polyneuropathy (distal symmetric polyneuropathy), as determined by the simplified screening criteria from the Working Group for Diabetic Neuropathy on 18 January 2002, partially modified version.

  Screening Criteria of Diabetic Polyneuropathy
  Prerequisite Condition:
  Must meet the following two items
  1. Diagnosis of diabetes
  2. Other neuropathies than diabetic neuropathy can be excluded

  Criteria:
  Meet any two of following three items
  1. Presence of symptoms considered to be due to diabetic polyneuropathy
  2. Decreased vibration in bilateral medial malleoli
  3. Decrease or disappearance of bilateral ankle reflex

  Notes:
  1. Symptoms considered to be due to diabetic polyneuropathy include:
     1) bilateral pain
     2) numbness, pain, paresthesia, or decreased sensation in the tips of toes and bottom of feet

     Must meet the above two items

     Excludes symptoms in only upper extremities or related only to cold, as with peripheral vascular disease
  2. Ankle reflex is examined on standing position on the knees
  3. Decreased vibration sense is considered ≤10 seconds by 128 Hz tuning fork.
  4. Take age into consideration in elderly subjects

8.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at Visit 1, and Visit 2, where indicated:

[8] Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted

[9] Are Lilly employees, or are employees of Shionogi, an alliance partner of Lilly, or are employees of a third-party organization (TPO) involved in this study

[10] Are currently enrolled in a clinical trial involving a study drug or nonapproved use of a drug or device (other than the study drugs used in this study), or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study

[11] Have been treated with other investigational drug(s) within 30 days immediately prior to Visit 1

[12] Have previously completed or withdrawn from any study investigating duloxetine or pregabalin or have previously been treated with duloxetine or pregabalin

[13] Have complications of serious cardiovascular, hepatic, renal, respiratory or hematological diseases, or symptomatic peripheral vascular diseases, and whose enrollment in this clinical trial is considered inappropriate

- "Serious" can be considered as a grade 3 AE as described in the Ministry of Health, Labour and Welfare-Pharmaceutical Affairs Bureau (MHLW-PAB) Notification No. 80 (29 June 1992): "Criteria for Severity Classification of Adverse Drug Reactions of Pharmaceutical Products."

[14] Have undergone renal transplant, or are currently undergoing renal dialysis.

[15] Have uncontrolled narrow-angle glaucoma, history of uncontrolled seizures, or uncontrolled or poorly controlled hypertension

[16] Glycemic control has been poor within 70 days immediately prior to Visit 1 (for example, ketoacidosis requiring hospitalization, or hypoglycemia that may cause consciousness disorder)

[17] Pregnant* or lactating female patients, or male patients who are planning for their partners to be or become a pregnant during the timeframe of the study

(* detailed information can be found in Attachment 2. Protocol HMHA Clinical Laboratory Tests)

[18] Have hypersensitivity to multiple medications

[19] Answered "yes" to either Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) or Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the Columbia-Suicide Severity Rating Scale (C–SSRS) or answered "yes" to any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act or behavior) on the "Suicidal Behavior" portion of the C–SSRS; and the ideation or behavior occurred within the past month

[20] Have past history of psychiatric diseases, such as depression, anxiety disorder, eating disorder, etc., that required drug therapy in the past 1 year, or who are currently having complications of these diseases or any history of manic psychosis or bipolar disorder

[21] Have MDD as determined using depression module of the Mini-International Neuropsychiatric Interview (MINI)

[22] Have complications of diseases that are considered to affect the assessment of diabetic peripheral neuropathic pain. For example, nerve diseases with pain other than diabetic peripheral neuropathic pain (cervical spondylosis, carpal tunnel syndrome, spinal canal stenosis, and post-herpetic pain), pain diseases other than nerve diseases (collagen diseases, gout, chronic obstructive arteriosclerosis, and arthritis), and other pain at the site of evaluation (skin diseases and traumatic injury) are excluded.

[23] Have neuropathic pain suspected to be caused by alcohol

[24] Have past history of drug abuse or dependence (including alcohol dependence) in the past 1 year, or who are currently having complication, thereof
[25] Considered unsuitable to participate in the study as judged by the investigator
[26] Have been treated with a monoamine oxidase (MAO) inhibitor(s) within 14 days immediately prior to Visit 2. Patients who visited the investigator site 14 days prior to Visit 2, those who have been treated with MAO inhibitors(s), thereafter, are excluded
[27] Have alanine aminotransferase (ALT) and aspartate aminotransferase (AST) at a level ≥100 U/L at Visit 1
[28] Have total bilirubin at a level ≥1.5 mg/dL at Visit 1
[29] Have creatinine clearance (CrCL), calculated by Cockroft-Gault, that is <1.0 mL/s (<60mL/min) at Visit 1
[30] Have a white blood cell (WBC) value <2500/mm^3, neutrophils <1500/mm^3, or platelets <100×103/mm^3 on their hematology tests at Visit 1
[31] Introduction of any treatments for diabetes, or a change in dosing regimen of any treatments for diabetes (exclude insulin treatment), or resumption of insulin treatment after Visit 1
[32] Have been treated with prohibited concomitant drug(s), or who have undergone prohibited concomitant treatment(s) after Visit 1
[33] Have taken restricted concomitant drugs 27 days immediately before Visit 1, with continued use of the restricted concomitant drug prior to Visit 1
[34] Have taken acetaminophen for 4 days or more 7 days immediately prior to Visit 2

8.2.1. Rationale for Exclusion of Certain Study Candidates

The majority of exclusions are for patient safety reasons, as well as compliance with the summary of product characteristics, and to minimize confounding effects on the study data. Exclusions [8] and [9] reduce the potential bias that may be introduced at the study site. Exclusions [10] and [11] exclude drugs that cannot be mapped to a standard drug dictionary or for which few data are known to analyze the potential relationship of AEs or drug interactions. Exclusion [12] eliminates patients who have participated in other duloxetine or pregabalin trials and/or have had previous exposure to duloxetine or pregabalin to minimize the potential response bias. Exclusions [13], [15], [16], [18], [21], [22], [23], [24], [25], [26], [27], [28], [29], and [30] eliminate potential safety issues. Exclusion [14] is included because patients with compromised renal function would need to have individualized dose adjustment for pregabalin, and this is not possible in this study. Exclusion [17] is intended to reduce potential risk to the infant by preventing lactation exposure, because risks to infants (as well as the fetus) are unknown. Exclusion [19] excludes patients with serious mental diseases. Exclusion [20] is to demonstrate independent effect on pain. Exclusions [31], [32], [33], and [34] are included because some treatments can interfere with pain evaluation.

8.3. Discontinuations

8.3.1. Discontinuation of Inadvertently Enrolled Patients

The criteria for enrollment must be followed explicitly. If the investigator site identifies a patient who did not meet enrollment criteria, and who was inadvertently enrolled, the sponsor must be notified. If the sponsor identifies a patient who did not meet enrollment criteria, and who was inadvertently enrolled, the investigator site will be notified. A discussion must occur between the sponsor clinical research physician or clinical research scientist and the investigator to determine whether the patient may continue in the study, with or without study drug. Inadvertently enrolled patients may be maintained in the study and on study drug when the Lilly clinical research physician or clinical research scientist agree with the investigator that it is medically appropriate for that patient. The patient may not continue in the study with or without study drug if the Lilly clinical research physician or clinical research scientist does not agree with the investigator's determination it is medically appropriate for the subject to continue. The investigator must obtain documented approval from the Lilly clinical research physician or clinical research scientist to allow the inadvertently enrolled patient to continue in the study with study drug.

8.3.2. Discontinuation of Study Drug

Discontinuation of the study drug for abnormal liver tests should be considered by the investigator when a patient meets one of the following conditions after consultation with the Lilly designated medical monitor:

- ALT or AST >8X upper limit of normal (ULN)
- ALT or AST >5X ULN for more than 2 weeks
- ALT or AST >3X ULN and total bilirubin level >2X ULN or prothrombin time >1.5X ULN
- ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Patients who discontinue the study drug early will have end-of-therapy procedures performed as shown in the Study Schedule (Attachment 1).

8.3.3. Patient Discontinuation from the Study

In addition, patients will be discontinued from the study in the following circumstances:

- Enrollment in any other clinical trial involving study drug or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Investigator Decision
    - The investigator decides that the patient should be discontinued from the study

  - If the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent

- Subject Decision
  - The patient requests to be withdrawn from the study
- Sponsor Decision
  - Lilly, Shionogi, or its designee stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP
- Adverse Event
  - If the investigator decides that the patient should be withdrawn because of an SAE or a clinically significant laboratory value, the study drug is to be discontinued and appropriate measures are to be taken. Lilly, Shionogi, or its designee is to be alerted immediately. Refer to Safety Evaluations Section 10.4.
- The patient experiences a clinically severe AE, in the opinion of the investigator, that would preclude further participation in the study, or the patient does not tolerate the planned dosages.
- The female patient is willing to become pregnant, or becomes pregnant. The male patient is willing to have a child.
- There is a significant protocol violation, as determined by the investigator or sponsor.
- The patient answers "yes" to either Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) or Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the C-SSRS during the study period, or answers "yes" to any of the suicide−related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act or behavior) on the "Suicidal Behavior" portion of the C-SSRS.
- If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from the study. In cases where there are ethical reasons to have the patient remain in the study, the investigator must obtain specific approval from a Lilly clinical research physician or clinical research scientist for the patient to continue in the study.

Patients who discontinue study early will have discontinuation procedures performed as shown in the Study Schedule (Attachment 1).

8.3.4. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, Shionogi, or its designee, the investigator, or the IRB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

8.3.5. Discontinuation of the Study

The study will be discontinued if Lilly, Shionogi, or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

9. Treatment

9.1. Treatments Administered

Information for study drugs is shown below.

Duloxetine:

- Name of the study drug: LY248686
- Generic name: Duloxetine hydrochloride (JAN)
- Chemical name: (+)-(S)-N-Methyl-3-(1-naphthyloxy)-3-(2-thienyl)propylamine hydrochloride
- Ingredient/content/formulation type: It is a dark brown, opaque, hard capsule packed with lipid-soluble granules containing 20 mg of duloxetine.
- Placebo of LY248686: A placebo capsule that is indistinguishable from LY248686 capsule.

Pregabalin:

- Generic name: Pregabalin
- Chemical name: (S)-3-(aminomethyl)-5-methylhexanoic acid
- Ingredient/content/formulation type: It is a hard capsule packed with 25 or 150 mg of pregabalin
- Placebo of pregabalin: A placebo capsule that is indistinguishable from pregabalin encapsulated capsule

This study involves a comparison of duloxetine (40 to 60 mg QD) given orally for 12 weeks to pregabalin (150 to 300 mg BID) given orally for 12 weeks. Table HMHA.1 shows the treatment regimens.

All duloxetine doses will be administered using 20-mg capsules (or matching placebo capsules, as applicable).

All pregabalin doses will be administered using over-encapsulated 25-mg and 150-mg capsules (or matching placebo capsules, as applicable).

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the investigational agent(s) to the patient and site personnel
- verifying that instructions are followed properly
- maintaining accurate records of study drug dispensing and collection
- returning all unused medication to Lilly, Shionogi, or its designee at the end of the study

Note: In some cases, sites may destroy the material if, during the investigator site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose clinical trial materials.

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the study drug so that the situation can be assessed.

Table HMHA.1. Treatment Regimens

Dose Regimen	Screening	Double-Blind Treatment				Tapering	Follow-up
	Period 1	Period 2-A		Period 2-B		Period 3	Period 4
	Dose	Dose Weeks 0 to 1	Dose Weeks 1 to 4	Dose Weeks 4 to 8	Dose Weeks 8 to 12	Dose Weeks 12 to 13	Dose Weeks 13 to 14
Duloxetine							
No dose increase[a]	N/A	20 mg/day	40 mg/day	40 mg/day	40 mg/day	20 mg/day	N/A
Dose increase at Week 4	N/A	20 mg/day	40 mg/day	60 mg/day	60 mg/day	40 to 20 mg/day[b]	N/A
Dose increase at Week 8	N/A	20 mg/day	40 mg/day	40 mg/day	60 mg/day	40 to 20 mg/day[b]	N/A
Pregabalin							
No dose increase[a]	N/A	150 mg/day	300 mg/day	300 mg/day	300 mg/day	150 mg/day	N/A
Dose increase at Week 4	N/A	150 mg/day	300 mg/day	450 mg/day	450 mg/day	300 to 150 mg/day[c]	N/A
Dose increase at Week 8	N/A	150 mg/day	300 mg/day	300 mg/day	450 mg/day	300 to 150 mg/day[c]	N/A
Dose increase at Weeks 4 and 8	N/A	150 mg/day	300 mg/day	450 mg/day	600 mg/day	300 to 150 mg/day[c]	N/A

Abbreviations: N/A = not available/not applicable.

[a] No dose increase during Period 2-B.

[b] 40 mg/day for the first 3 days of the 1-week tapering period and then 20 mg/day for the last 4 days.

[c] 300 mg/day for the first 3 days of the 1-week tapering period and 150 mg/day for the last 4 days.

9.2. Materials and Supplies

Lilly, Shionogi, or its designee will provide the following study materials:

- 20-mg capsules of duloxetine hydrochloride
- 25-mg and 150-mg over-encapsulated capsules of pregabalin
- placebo capsules identical in appearance to duloxetine capsules
- placebo capsules identical in appearance to pregabalin over-encapsulated capsules

Duloxetine, pregabalin, and matching placebo capsules will be provided to patients in the study.

All study drugs will be handled, stored (for example, at room temperature), and used in accordance with this protocol and the respective PI for each study drug. Study drug will be dispensed to the patient at the study site. Patients will be given instructions on how and when to take each dose. Study drug packaging will be labeled with a unique identifier for drug accountability. Study drug packages will contain additional capsules to allow for permitted deviations in visit intervals. Clinical trial materials will be labeled according to Japan's regulatory requirements.

Patients who are discontinuing from the study should attend the site and will receive separate drug supplies for tapering down of study drug (see Section 9.5.1).

9.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be randomized to double-blind treatment at Visit 2. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign blisterpacks containing double-blind study drug to each patient. The appropriate number of blisterpacks will be dispensed at Visit 2, Visit 4, and Visit 5, depending on each dose regimen. Site personnel will confirm that they have located the correct blisterpacks by entering a confirmation number found on the blisterpacks into the IWRS.

Randomization will be stratified by baseline weekly mean of the 24-hour average pain score measured using the 11-point NRS in the dairy patient diary (<6, ≥6) and duration of DPNP (<2 years, ≥2years).

9.4. Rationale for Selection of Doses in the Study

The doses selected for this study are based on the current licensed dosages in Japan (see Section 7.2).

9.5. Selection and Timing of Doses

Patients who take part in all treatment phases will receive double-blind treatment for 12 weeks during Period 2 and for 1 week during Period 3. The number of capsules will vary after Visit 4 (Week 4), depending on whether or not patients receive dosage increases at Visit 4 and Visit 5 (Week 8). Table HMHA.2 depicts the number of capsules by dose regimen, treatment, and time of day. Capsules will contain active study drug (duloxetine or pregabalin) or placebo (see Section 9.2).

Table HMHA.2. Number of Capsules by Dose Regimen, Treatment, and Time of Day

Dose Regimen Time	Morning			Evening		
	Capsule 1	Capsule 2	Total Number of Capsules	Capsule 1	Capsule 2	Total Number of Capsules
No Dose Increase at Week 4 or 8						
Weeks 0 to 1	○	□□□	4	-	□□□	3
Weeks 1 to 4	○○	□	3	-	□	1
Weeks 4 to 8	○○	□	3	-	□	1
Weeks 8 to 12	○○	□	3	-	□	1
Weeks 12 to 13 (First 3 days)	○	□□□	4	-	□□□	3
Weeks 12 to 13 (last 4 days)	○	□□□	4	-	□□□	3
Dose Increase at Week 4						
Weeks 0 to 1	○	□□□	4	-	□□□	3
Weeks 1 to 4	○○	□	3	-	□	1
Weeks 4 to 8	○○○	□□□□	7	-	□□□□	4
Weeks 8 to 12	○○○	□□□□	7	-	□□□□	4
Weeks 12 to 13 (First 3 days)	○○	□	3	-	□	1
Weeks 12 to 13 (last 4 days)	○	□□□	4	-	□□□	3
Dose Increase at Week 8						
Weeks 0 to 1	○	□□□	4	-	□□□	3
Weeks 1 to 4	○○	□	3	-	□	1
Weeks 4 to 8	○○	□	3	-	□	1
Weeks 8 to 12	○○○	□□□□	7	-	□□□□	4
Weeks 12 to 13 (First 3 days)	○○	□	3	-	□	1
Weeks 12 to 13 (last 4 days)	○	□□□	4	-	□□□	3
Dose Increases at Week 4 and Week 8						
Weeks 0 to 1	○	□□□	4	-	□□□	3
Weeks 1 to 4	○○	□	3	-	□	1
Weeks 4 to 8	○○○	□□□□	7	-	□□□□	4
Weeks 8 to 12	○○○	□□	5	-	□□	2
Weeks 12 to 13 (First 3 days)	○○	□	3	-	□	1
Weeks 12 to 13 (last 4 days)	○	□□□	4	-	□□□	3

○: Duloxetine 20 mg (or Duloxetine placebo), □: Pregabalin 25 or 150 mg (or Pregabalin placebo)
Patients assigned to Duloxetine will take active Duloxetine and Pregabalin placebo, and patients assigned to active Pregabalin will take Duloxetine placebo and Pregabalin.

For all periods during which patients receive treatment, doses should be taken daily at approximately the same time of day if possible. Capsules should be swallowed whole and

should not be crushed or broken. Patients should take the capsules after a meal (breakfast and dinner).

Patients will be asked to retain the empty packaging and to return it, together with any unused study drugs, at each visit after the start of dosing. Returned packaging and study drugs will be checked by staff at the investigational site at each applicable visit. Details of all study drugs dispensed and returned will be recorded (see Section 9.9).

Patients are to remain on a stable dose of duloxetine or pregabalin until the required dosage increase at Week 1 and the possible dose increases at Visit 4 (Week 4) and Visit 5 (Week 8). If patients experience significant intolerability during dose increases, they are to be discontinued from the study (with appropriate tapering; see Section 9.5.1). This assessment of intolerability will be made by the investigator and the patient. For patients discontinuing from the study, separate packages will be provided to taper the dose, if necessary.

Patients will be informed that they can contact the investigational site at any time during treatment to discuss side effects and tolerability issues.

9.5.1. Special Treatment Considerations

To help minimize the risk of discontinuation reactions, study drug doses will be tapered for selected dose regimens during Period 3 (Visit 6 [Week 12] to Visit 7 [Week 13]) before study drugs are discontinued. The following tapering regimes will apply to patients whose final study drug dose, during Period 2, were duloxetine 40/60 mg/day or pregabalin 300/450/600 mg/day.

If a patient discontinues during the first week of double-blind treatment, his/her medication should be discontinued abruptly.

If a patient discontinues during or after the second week of double-blind treatment, his/her medication should be tapered over 7 days as follows, depending on the dosage when they discontinue.

- Duloxetine final dose of 40 mg/day
  - 20 mg/day for 7 days
- Duloxetine final dose of 60 mg/day
  - 40 mg/day for the first 3 days
  - 20 mg/day for the last 4 days
- Pregabalin final dose of 300 mg/day
  - 150 mg/day for 7 days
- Pregabalin final dose of 450 mg/day
  - 300 mg/day for the first 3 days
  - 150 mg/day for the last 4 days
- Pregabalin final dose of 600 mg/day
  - 300 mg/day for the first 3 days
  - 150 mg/day for the last 4 days

A patient may be discontinued from the study without being tapered off his/her medication if the patient refuses to be tapered, or in the case of a SAE, for patient safety or ethical reasons.

Patients who are discontinuing from the study must attend the study site for an early discontinuation (ED) visit and to receive study drug for dose tapering (if applicable). These patients must attend the study site for a follow-up visit (Visit 301) 1 week after the end of study drug tapering (Visit 7). For patients who discontinue the study drug without tapering, they must still attend the study site for an ED visit and a follow-up visit (Visit 301).

Restricted medications are summarized in Protocol Addendum F1J-JE-HMHA (1413N0841).

9.6. Continued Access to Study Drug

After the conclusion of the study, access to each of the study drugs is possible through commercial sources. Treatment of patients after the end of the study will be at the discretion of the treating physician.

9.7. Blinding

This is a double-blind study. Double dummy technique is used for retaining the blind. To assure the blinding of the study, a minimum number of Lilly Japan personnel will see the randomization table and treatment assignments before the study is completed (see Section 9.7.1).

9.7.1. Unbliding for SAEs

CCI

CCI [redacted]

CCI [redacted]

[redacted]

9.7.2. Emergency unblinding for AEs

Emergency unblinding for AEs may be performed through an IWRS, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. All communications resulting in an unblinding event are recorded by the IWRS.

If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from the study. In cases where there are ethical reasons to have the patient

remain in the study, the investigator must obtain specific approval from a Lilly clinical research physician or clinical research scientist for the patient to continue in the study.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Lilly clinical research physician prior to unblinding a patient's treatment assignment. If a patient's treatment assignment is unblinded, Lilly and Shionogi must be notified immediately.

9.8. Concomitant Therapy

The list of prohibited and limited medications and therapies is provided in Protocol Addendum F1J-JE-HMHA (1413N0841).

Concomitant medications will be recorded on electronic case report forms (eCRFs), including dose and duration of treatment. In addition, medications that are ongoing at the time of Visit 1 will be collected as concomitant medications in the eCRF. Patients requiring excluded concomitant drugs will be discontinued from the study, unless approval has been obtained from the sponsor clinical research physician or clinical research scientist.

Patients will be instructed to consult with the investigator or other site personnel before taking any new prescribed medications, over-the-counter medications, or supplements/herbal preparations. If an investigator directs a patient to discontinue any medication in order to comply with this protocol, this instruction should take place only after the patient has signed the ICF.

9.9. Treatment/Diary Compliance

Patient compliance with study medication will be assessed at each visit. Compliance will be assessed by direct questioning and counting returned tablets. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

Diary completion will directly affect primary efficacy data collection; thus, the status of compliance with diary completion will be assessed at each visit from Visit 2 to Visit 6. A patient will be considered to be compliant with the diary at each visit if he/she has completed at least 80% of the diaries over the total days since the last visit.

Compliance for each visit interval is defined as taking between 80% and 120% of the study drug dosage prescribed for that interval. The first time a patient is noncompliant, the patient will be counseled on the importance of taking the prescribed amount of study drug(s). The second time (either consecutive or nonconsecutive) that a patient is noncompliant, Lilly or its representative will be notified.

Patients who are significantly noncompliant may be discontinued from the study. A patient will be considered significantly noncompliant if he/she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication.

Patients should be instructed to return all study drug packaging and unused study drugs and supplies to the study site at each visit. The study site will keep a record of all study drugs dispensed to and returned by the patients throughout the study. The study site will return all unused study dugs to Lilly or its designee. The investigator (or designee) at each investigational site will be responsible for keeping a drug accountability log. A drug reconciliation will be performed as appropriate, for example, throughout, and at the end of the study.

10. Efficacy, Health Outcome/Quality of Life Measures, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

Study procedures and their timing (including tolerance limits for timing) are summarized in the Study Schedule (Attachment 1).

10.1. Efficacy Measures

10.1.1. Primary Efficacy Measure

The primary efficacy measure will be the 11-point NRS in the daily patient diary, ranging from 0 (no pain) to 10 (pain as bad as you can imagine). The 11-point NRS measures the severity of pain over the previous 24 hours. Patients will be asked to provide 24-hour average pain, 24-hour worst pain and night pain scores in the daily patient diary. Among these, the weekly mean of the 24-hour average pain score will be the primary endpoint, and the other 2 items will be secondary endpoints.

10.1.2. Secondary Efficacy Measures

The following secondary efficacy measures will be collected at the times shown in the Study Schedule (Attachment 1).

- **BPI Short Form (BPI-SF):** The BPI-SF (Cleeland and Ryan 1994) is a self-reported instrument that measures the severity of pain and the interference of pain on function. There are a total of 11 questions on the form, which are self-rated by the patient. Each question is scored on an 11-point scale, ranging from 0 to 10.
    - **BPI pain severity portion**: There are 4 questions, which assess the severity of worst pain and least pain in the past 24 hours, average pain, and the pain experienced by the patient "right now." The scores range from 0 (no pain) to 10 (pain as bad as you can imagine).
    - **BPI interference portion**: There are 7 questions, which assess how pain has interfered with the patient's functioning in the past 24 hours on general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. The interference scores range from 0 (does not interfere) to 10 (completely interferes).
- The 24-hour worst pain and the night pain scores measured using the 11-point NRS in the daily patient diary (see Section 10.1).
- **Patient Global Impression of Improvement (PGI-I):** The PGI-I (Guy 1976) assessments will be completed by the patient. The patient will record how he/she perceives the degree of improvement (or worsening) at the time of assessment since taking treatment. The score ranges from 1 (very much better) to 7 (very much worse).

- **Neuropathic Pain Symptom Inventory (NPSI):** The NPSI (Bouhassira et al. 2004) questionnaire is a 12-item self-administered questionnaire that will be completed by the patient. It assesses 5 different dimensions of neuropathic pain: burning spontaneous pain, pressing spontaneous pain, paroxysmal pain, evoked pain, and paresthesias/dysesthesias.
- **Clinical Global Impression of Improvement (CGI-I):** The CGI-I (Guy 1976) will be completed by the study physician in the presence of the patient or after having been in the presence of the patient. The clinician will record the degree of the patient's improvement (or worsening) since taking treatment (Visit 2), regardless of whether the improvement (or worsening) is thought to be entirely due to the drug treatment. Improvement is rated on a 7-point scale, ranging from 1 (very much improved) to 7 (very much worse).
- **Beck Depression Inventory-II (BDI-II):** The BDI-II (Beck et al. 1996) is a self-administered scale that serves as an indicator of the presence and degree of depressive symptoms consistent with those of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision (DSM-IV-TR). The BDI-II contains 21 items that characterize how the patient was feeling in the past 2 weeks.

10.2. Health Outcome/Quality of Life Measures

The following secondary health outcome measure will be collected at the times shown in the Study Schedule (Attachment 1).

- **EuroQol 5 Dimension (EQ-5D):** The EQ-5D (EuroQol 1990) is a self-reported, 5-item scale used to assess the patient's health utility (mobility, self-care, usual activities, pain and discomfort, and depression/anxiety). Scoring is on a 3-point scale. In addition, a Quality of Life "thermometer" visual analog scale (VAS) is presented that is rated from 0 to 100.

10.3. Other Measures

The following measures will be collected at baseline (Visit 2) only as shown in the Study Schedule (Attachment 1):

- **Patient Global Impression of Severity (PGI-S):** The PGI-S (Guy 1976) assessments will be completed by the patient. The patient will record how he/she feels at the current time. It will be completed at baseline (Visit 2) only. Severity is rated on a 7-point scale, ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill patients).
- **Clinical Global Impression of Severity (CGI-S):** The CGI-S (Guy 1976) will be completed by the study physician in the presence of the patient, or after having been in the presence of the patient. The clinician will record how ill the patient is at the current time, in relation to the clinician's total experience with this patient population. It will be completed at baseline (Visit 2) only. Severity is rated on a 7-point scale, ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill patients).

- **Mini-International Neuropsychiatric Interview (MINI):** The MINI (Sheehan et al. 1998) is a short structured diagnostic interview, developed jointly by psychiatrists and clinicians in the United States (US) and Europe, for DSM-IV-TR and International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) psychiatric disorders. With an administration time of approximately 15 minutes, it was designed to meet the need for a short, but accurate, structured psychiatric interview for multicenter clinical trials. Only the MDD module of the MINI will be completed at baseline (Visit 2).

10.4. Safety Evaluations

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to the study treatment or the study, or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

10.4.1. Adverse Events

The sponsor has standards for reporting AEs that are to be followed, regardless of applicable regulatory requirements that may be less stringent.

Cases of pregnancy that occur during maternal or paternal exposures to study drug should be reported. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation.

Study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

After the ICF is signed, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs. All AEs related to protocol procedures are reported to the sponsor via electronic data entry (Inform). In addition, all AEs occurring after the patient receives the first dose of study drug must be reported to the sponsor or its designee via electronic data entry.

Any clinically significant findings from ECGs, labs, vital sign measurements, and other procedures that result in a diagnosis should be reported to sponsor.

Investigators will be instructed to report to the sponsor their assessment of the potential relatedness of each AE to protocol procedure, studied disease state, study drug, via electronic data entry/designated data transmission methods.

The investigator decides whether he or she interprets the observed AEs as either related to disease, to the study medication, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to the study drug, the following terminologies are defined:

- **Related**: a direct cause-and-effect relationship between the study treatment and the AE is likely
- **Possibly related**: a cause-and-effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible
- **Unrelated**: without question, the AE is definitely not associated with the study treatment

As per sponsor's SOPs, all "related" and "possibly related" AEs and SAEs will be defined as related to study drug.

Adverse events that have occurred during the time from Visit 1 to the follow-up visit (Visit 301), are surveyed (Attachment 1).

10.4.1.1. Serious Adverse Events

Serious adverse event collection begins after the patient has signed informed consent and has received study drug. If a patient experiences an SAE after signing informed consent, but prior to receiving study drug, the event will NOT be reported as serious, unless the investigator feels the event may have been caused by a protocol procedure. Serious adverse events will be reported the same period for AE report.

Planned surgeries should not be reported as SAEs, unless the underlying medical condition has worsened during the course of the study.

Study site personnel must alert Lilly of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Lilly should report all SAE information to Shionogi for their safety evaluations within 48 hours of Lilly awareness of the event.

An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate

medical judgment, they may jeopardize the patient, and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse events that occur up to and including the patient's last study visit will be collected, regardless of the investigator's opinion of causation, in the clinical data collection database and the pharmacovigilance system at Lilly. The investigator does not need to actively monitor patients for AEs once the trial has ended, unless provided otherwise in the protocol. If an investigator becomes aware of SAEs occurring to a patient after the patient's participation in the trial has ended, the investigator should report the SAEs to Lilly, regardless of the investigator's opinion of causation, and the SAEs will be entered in the pharmacovigilance system at Lilly.

10.4.2. Other Safety Measures

10.4.2.1. Electrocardiograms

For each patient, 12-lead digital electrocardiograms (ECGs) will be collected locally at the investigative site according to the Study Schedule (Attachment 1) as single ECG evaluation. Patients must be supine for approximately 5 to 10 minutes before ECG collection, and remain supine, but awake, during ECG collection.

Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs than expected at a particular time point is allowed when needed to ensure high quality records.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, to determine whether the subject meets entry criteria and for immediate subject management, should any clinically relevant findings be identified.

The investigator (or qualified designee) must document his/her review of the ECG printed at the time of evaluation.

Electrocardiograms will be evaluated for patients who have a risk of cardiovascular events based on the investigator's decision at baseline to determine subject eligibility, at Visit 7 during the safety evaluation for tapering/discontinuation, or at early discontinuation. Electrocardiograms may be obtained at additional times depending on the investigator's decision.

10.4.2.2. Columbia Suicide Severity Rating Scale (C–SSRS) and Self-harm Follow-up Form

The C-SSRS (Posner et al. 2007, 2011) captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. The scale includes suggested questions to solicit the type of information needed to determine if a suicide-related thought or behavior occurred. The C-SSRS will be administered by an investigator/study physician according to the Study Schedule (Attachment 1). The tool was developed by the National Institutes of Mental Health (NIMH) trial group for the purpose of being a counterpart to the Food and Drug Administration's (FDA's) categorization of suicidal events.

10.4.2.3. Fall Questionnaire

According to the Study Schedule (Attachment 1), patients will respond yes/no to a simple unpublished questionnaire that solicits fall events. If the patient responds yes, additional questions will be asked regarding the status of the patient when the fall occurred, whether or not the patient used walking aids, what physical complaints the patient had at the time of the fall, and the outcome of the fall. If the patient responds yes on the questionnaire, the event will be reported as an AE or SAE depending on the outcome of the fall.

10.4.3. Safety Monitoring

The Lilly clinical research physician or clinical research scientist will monitor safety data throughout the course of the study.

Edema and its related events will be monitored carefully, per PMDA, because angiotensin converting enzyme inhibitors and thiazolidines are not prohibited in this study. There are precautions for these drugs in the pregabalin PI; however, there is no obvious evidence for the relationship between these drugs and edema. Moreover, there is no report that these drugs will influence the efficacy evaluation for duloxetine and pregabalin.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly clinical research physician will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist and Shionogi.

If a study patient experiences elevated ALT or AST >3X ULN, or elevated total bilirubin >2X ULN, clinical and laboratory monitoring should be initiated by the investigator. Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with Lilly regarding collection of specific recommended clinical information and follow-up laboratory tests. See Attachment 3.

10.4.4. Complaint Handling

Lilly collects product complaints on study drugs and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

All product complaints associated with material packaged, labeled, and released by the sponsor will be reported.

The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- Recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- Faxing the completed product complaint form within 24 hours to Lilly or its designee

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

10.5. Sample Collection and Testing

Attachment 1 lists the schedule for sample collections in this study.

Attachment 2 lists the laboratory tests that will be performed for this study.

10.5.1. Samples for Study Qualification and Health Monitoring

Blood and urine samples will be collected to determine whether patients meet inclusion/exclusion criteria and to monitor patient health.

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run, or to retain the samples until the end of the study to confirm that the results are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

10.6. Appropriateness of Measurements

The measures of efficacy and safety are standard measures used in clinical trials of DPNP and depression and are well documented and reliable.

11. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- Provide instructional material to the study sites, as appropriate
- Sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the eCRFs, and study procedures.
- Make periodic visits to the study site
- Be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- Review and evaluate eCRF data and use standard computer edits to detect errors in data collection
- Conduct a quality review of the database

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Shionogi, Lilly, or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable IRBs with direct access to original source documents.

11.1. Data Capture System

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Electronic patient-reported outcome (ePRO) measures are entered into an ePRO instrument at the time that the information is obtained. In these instances where there is no prior written or electronic source data at the site, the ePRO instrument record will serve as the source.

In this study, the patient diary will be reported via ePRO. An 11-point NRS in the daily patient diary, such as the 24-hour average pain and 24-hour worst pain and night pain scores, will be entered into an ePRO.

If ePRO records are stored at a TPO, investigator sites will have continuous access to the source documents during the study and will receive an archival copy at the end of the study for retention.

Any data for which the ePRO instrument record will serve to collect source data will be identified and documented by each site in that site's study file.

Case report form data collected by the TPO will be encoded by the TPO and stored electronically in the TPO's database system. Validated data will subsequently be transferred to Lilly's data warehouse, using standard Lilly file transfer processes.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly's database.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

Approximately 410 (205 per arm) patients will be randomized.

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 efficacy of duloxetine and pregabalin are equal and that the common standard deviation (SD) of the primary endpoint is 1.82 with a non-inferiority margin of 0.51, 201 patients per group (402, in total) would have a statistical power of 80% to confirm the noninferiority with a 1-sided significance level of 0.025.

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% confidence interval (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.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly.

Efficacy analyses will be conducted on the full analysis set (FAS). 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.

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.

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.

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 clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

12.2.2. Patient Disposition

All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given. The reasons for patient discontinuation (completed the study, discontinued due to AEs, discontinued due to lack of efficacy, etc) will be summarized with counts and percentages within each of the 2 treatment groups. Treatment-group differences will be evaluated using Fisher's exact tests.

12.2.3. Patient Characteristics

Patient characteristics, disease severity, and history will be summarized by treatment group.

12.2.4. Concomitant Therapy

Previous medications (that is, those taken and stopped before baseline) and concomitant medication used during the study will be summarized by treatment group. For previous and concomitant medications, treatment group differences in the frequency of usage for each medication will be analyzed by Fisher's exact test.

12.2.5. Treatment/Diary Compliance

At each visit, patients' compliance with the study medication 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. Percentage compliance will be summarized using means, standard deviations, medians etc. by treatment group and visit and additionally, counts and percentages of patients with compliance <80%, between 80% and 120%, and so forth, will be presented.

In addition, percentage of diary completion will be summarized using means, standard deviations, medians etc. by treatment group and visit and percentages of patients with compliance <80%, ≥80%, will be presented.

12.2.6. 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.

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 (Lu and Mehrotra 2010) will 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 will be used. Both analyses will be performed as a secondary analysis to examine the robustness of the primary analysis result.

- The last observation carried forward (LOCF) method for all the missing cases
- The baseline observation carried forward (BOCF) method for the patients who discontinued due to treatment-related reasons, such as AE or lack of efficacy, and the LOCF method for all the other missing cases

12.2.7. Efficacy Analyses

The secondary efficacy objectives will be addressed by conducting MMRM and/or ANCOVA analyses (as described in Section 12.2.6, 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:

- 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
- From 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

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

12.2.8. Health Outcome/Quality of Life Analyses

The secondary efficacy objectives for health outcome/quality of life measures will be addressed by conducting ANCOVA analyses (as described in Section 12.2.6) to compare treatment differences on the EQ-5D.

12.2.9. Safety Analyses

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

For key variables, statistical comparison between treatments will be conducted. For binomial data, such as the proportion of patients with TEAEs, etc, Fisher's exact test will be used. For continuous data, such as change from baseline-to-endpoint (LOCF) in laboratory measurements, etc, ANCOVA, including treatment and baseline value in the model, will be used.

12.2.10. 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.

Unblinding details are specified in the unblinding plan section of the statistical analysis plan (SAP) or a separate unblinding plan document.

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1. Informed Consent

The investigator is responsible for ensuring that the patient understands the potential risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

The ICF will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study, and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of study drug.

13.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are used at investigative sites(s). All ICFs must be compliant with the ICH guideline on GCP.

Documentation of IRB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). The IRB(s) will review the protocol as required.

The study site's IRB(s) should be provided with the following:

- current PI and updates during the course of the study
- ICF
- relevant curricula vitae

13.3. Regulatory Considerations

This study will be conducted in accordance with:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines
- International Conference on Harmonisation (ICH) GCP Guideline [E6]
- applicable laws and regulations

The investigator or designee will promptly submit the protocol to applicable IRB(s).

Some of the obligations of the sponsor will be assigned to a TPO.

An identification code assigned by the investigator to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting AEs and/or other trial-related data.

13.3.1. Investigator Information

Physicians with a specialty in internal medicine or diabetes will participate as investigators in this clinical trial.

13.3.2. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his/her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

13.3.3. Final Report Signature

The clinical study report coordinating investigator will sign the final clinical study report for this study, indicating agreement that, to the best of his/her knowledge, the report accurately describes the conduct and results of the study.

An investigator will be chosen by Lilly to serve as the clinical study report coordinating investigator.

The sponsor's responsible medical officer and statistician will approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

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Attachment 1. Protocol HMHA Study Schedule

Study Schedule, Protocol F1J-JE-HMHA (1413N0841)

Perform procedure as indicated.

	Period 1 Screening		Period 2 Treatment					Period 3 Tapering	Period 4 Follow up
Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**		**Visit 7**	**Visit 301**
Week	**Weeks -2 to -1**	**Week 0**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**ED**	**Week 13/ discontinuation[a]**	**Week 14/ discontinuation[b]**
Day	**Day -14 to -7**	**Day 0**	**Day 14**	**Day 28**	**Day 56**	**Day 84**	**-**	**-**	**-**
Allowable range	**-**	**-**	**± 7 days**	**± 7 days**	**± 7 days**	**+ 7 days**	**+ 3 days[c]**	**+ 3 days**	**+ 3 days**
Patient characteristics/ diagnosis									
Consent obtainment	Y								
Patient characteristics	Y								
Diagnosis of diabetic neuropathy	Y								
Past history/ complications	Y	Y							
Treatments									
Drug allocation		Y							
Prescription of the investigational drugs		Y	Y	Y	Y	Y	Y		
Recovery of the investigational drugs/ confirmation of remaining drugs			Y	Y	Y	Y	Y	Y	
Concomitant (previous) drugs/treatments	Y	Y	Y	Y	Y	Y	Y	Y	
Efficacy evaluation									
11-point NRS in the daily patient diary 24-hour average pain Worst pain Night pain	←						→		
PGI-S		Y							
PGI-I			Y	Y	Y	Y	Y		
BPI-SF		Y	Y	Y	Y	Y	Y		
BDI-II		Y		Y	Y	Y	Y		
MINI		Y							
CGI-S		Y							
CGI-I			Y	Y	Y	Y	Y		

	Period 1 Screening		Period 2 Treatment					Period 3 Tapering	Period 4 Follow up
Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**		**Visit 7**	**Visit 301**
Week	**Weeks -2 to -1**	**Week 0**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**ED**	**Week 13/ discontinuation[a]**	**Week 14/ discontinuation[b]**
Day	**Day -14 to -7**	**Day 0**	**Day 14**	**Day 28**	**Day 56**	**Day 84**	**-**	**-**	**-**
Allowable range	**-**	**-**	**± 7 days**	**± 7 days**	**± 7 days**	**+ 7 days**	**+ 3 days[c]**	**+ 3 days**	**+ 3 days**
NPSI		Y				Y	Y		
EQ-5D		Y				Y	Y		
Safety evaluation									
Adverse events	←								→
Hematology/clinical chemistry	Y			Y	Y	Y[e]	Y[f]	Y	
HbA1c[d]	Y			Y	Y	Y	Y[f]	Y	
Urinalysis	Y			Y	Y		Y	Y	
CrCL	Y								
Pregnancy test	Y	The test is performed, as appropriate, when the possibility of pregnancy is suspected.							
Sitting blood pressure/heart rate	Y	Y	Y	Y	Y	Y	Y	Y	
Electrocardiography[g]	Y						Y	Y	
C-SSRS	Y	Y	Y	Y	Y	Y	Y	Y	
Body weight		Y		Y		Y	Y	Y	
Fall Questionnaire		Y	Y	Y	Y	Y	Y	Y	

Abbreviations: BDI-II = Beck Depression Inventory-II; BPI-SF = Brief Pain Inventory-Short Form; CGI-I = Clinical Global Impression of Improvement; CGI-S = Clinical Global Impression of Severity; CrCL = Creatinine Clearance; C-SSRS = Columbia Suicide Severity Rating Scale; EQ-5D = EuroQol 5 Dimension; ED = Early Discontinuation; MINI = Mini-International Neuropsychiatric Interview; NPSI = Neuropathic Pain Syndrome Inventory; NRS = numeric rating scale; PGI-I = Patient Global Impression of Improvement; PGI-S = Patient Global Impression of Severity.

[a] Visit 7 occurs 7 days (+3) after Visit 6 or early discontinuation visit. Patients who discontinue the study drug without tapering do not require this visit. (See Section 9.5.1.)

[b] Visit 301 occurs 7 days (+3) after Visit 7 or ED Visit without tapering.

[c] ED is considered as the same day of the last administration. Variables for ED visit will be evaluated within 3 days after the last administration.

[d] When there are multiple HbA1c values measured at different institutes, the value measured at the same institute at Visit 1 is used for this eligibility judgment. If both values measured by the central laboratory are available, the most recent data should be used for this eligibility judgment.

[e] Glucose (fasting), Clinical chemistry only.

[f] This will be applied to patients who discontinue the study without tapering.

[g] ECG will be evaluated for patients who have a risk of cardiovascular events based on the investigator's decision.

Attachment 2. Protocol HMHA Clinical Laboratory Tests

Clinical Laboratory Tests (collected centrally)

Hematology:	**Clinical Chemistry:**
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte (red blood cell) count (RBC)	Potassium
Leukocyte (white blood cell) count (WBC)	Chloride
Neutrophils, segmented	Total bilirubin
Lymphocytes	Direct bilirubin
Monocytes	Alkaline phosphatase
Eosinophils	Alanine aminotransferase (ALT)
Basophils	Aspartate aminotransferase (AST)
Platelets	Gamma-glutamyltransferase (GGT)
	Lactate Dehydrogenase (LDH)
Urinalysis:	Total protein
Protein	Blood urea nitrogen (BUN)
Glucose	Creatinine
Blood	Uric acid
Urobilinogen	Calcium
Albumin	Glucose[c]
Creatinine	Albumin
Albumin- Creatinine ratio	Total cholesterol
	Low-density lipoprotein- (LDL-) cholesterol
Serum Pregnancy Test[a]	High-density lipoprotein- (HDL-) cholesterol
	Triglyceride (TG)
Others	Creatine kinase (CK)
Hemoglobin A1c (HbA1c)	
Creatinine clearance[b]	

[a] The serum pregnancy test applies to females of child-bearing potential (not surgically sterilized and between menarche and 1-year postmenopausal) only. Patients, who have test negative for pregnancy at the time of screening (Visit 1) based on this serum pregnancy test, are eligible for this study.

[b] Cockcroft-gault method will be used for estimating the Creatinine clearance.

[c] Glucose can be evaluated with the random glucose tests except for Visit 6.

Attachment 3. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow up with patients in consultation with the Lilly, or its designee, clinical research physician.

Hepatic Monitoring Tests (collected centrally)

Hepatic Hematology	**Haptoglobin**
Hemoglobin	
Hematocrit	**Hepatic Coagulation**
Erythrocyte (red blood cell) count (RBC)	Prothrombin Time
Leukocyte (white blood cell) count (WBC)	Prothrombin Time, International Normalized Ratio (INR)
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, immunoglobulin (Ig) M
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
Alanine aminotransferase (ALT)	**Anti-nuclear antibody**
Aspartate aminotransferase (AST)	
Gamma-glutamyltransferase (GGT)	**Anti-smooth muscle antibody**
Creatinine kinase (CK)	

Attachment 4. Protocol Amendment F1J-JE-HMHA (1413N0841) (b) Summary [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]

Overview

Protocol F1J-JE-HMHA (1413N0841) [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] has been amended. The new protocol is indicated by amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- Based on a request from PMDA, the detailed descriptions regarding the process of unblinding by Lilly Japan personnel for the purpose of reporting SAE information to regulatory authorities and a manufacturer overseas during the study period are added to clarify that blinding is assured in the study.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

9.7. Blinding

This is a double-blind study. Double dummy technique is used for retaining the blind. ~~To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete.~~ To assure the blinding of the study, a minimum number of Lilly Japan personnel will see the randomization table and treatment assignments before the study is completed (see Section 9.7.1).

9.7.1. Unbliding for SAEs

CCI

[redacted]

CCI [redacted]

9.7.2. Emergency unblinding for AEs

Emergency unblinding for AEs may be performed through an IWRS, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. All communications~~calls~~ resulting in an unblinding event are recorded ~~and reported~~ by the IWRS.

13.3. Regulatory Considerations

This study will be conducted in accordance with:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and ~~Council for International Organizations of Medical Sciences (~~CIOMS~~)~~ International Ethical Guidelines

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