Official Title: A Phase 2, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of LX9211 in the Treatment of Diabetic Peripheral Neuropathic Pain (RELIEF-DPN 1)

NCT Number: NCT04455633

Document Date: SAP Version 3: 07-June-2022

16.1.9 Documentation of Statistical Methods

Statistical Analysis Plan – Version 3.0 (07 June 2022)

Qualitativie Report (02 April 2020)

Statistical Analysis Plan

Lexicon Pharmaceuticals, Inc.

Protocol No.: LX9211.1.201-DPN

A Phase 2, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of LX9211 in the Treatment of Diabetic Peripheral Neuropathic Pain (RELIEF-DPN 1)

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Labcorp CDCS
Clinical Development Commercialization Services

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Reviewers

The following reviews of the statistical analysis plan (SAP) were conducted:

Name and Title	Role	Version Last Reviewed	Company/ Organization
[redacted]	Peer Review Statistician	3.0	Labcorp
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	QC Reviewer	3.0	Labcorp
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	[redacted] Pre-Clinical Development	2.0	Lexicon
	Project Manager	2.0	Lexicon

Glossary of Abbreviations

Abbreviation	Term
A1C	hemoglobin A1C
ADPS	average daily pain score
AE	adverse event
ALT	alanine transaminase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate transaminase
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
BP	blood pressure
BPI	brief pain inventory
BPI-DPN	Brief Pain Inventory - short form for diabetic peripheral neuropathy
BUN	blood urea nitrogen
C_{trough}	trough plasma concentrations
CBC	complete blood count
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CPK	creatinine phosphokinase
CRU	clinical research unit
DMC	Data Monitoring Committee
DPN	diabetic peripheral neuropathy
DPNP	diabetic peripheral neuropathic pain
ECG	electrocardiogram
eCRF	electronic case report form
HADS	Hospital Anxiety and Depression Scale
HDL	high-density lipoprotein
ICF	informed consent form
In	inches
ITT	Intent-to-Treat
IXRS	Interactive Voice/Web Response System
KM	Kaplan-Meier
Lbs	pounds
LDL	low-density lipoprotein
LS	least squares
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model for repeated measurements
MNAR	missing not at random
mITT	Modified Intent-to-treat
NPSI	Neuropathic Pain Symptom Inventory
NRI	non-responder imputation
OC	observed cases

PGIC	Patient Global Impression of Change
PE	physical examination
PK	pharmacokinetic(s)
PMM	pattern-mixture model
PP	Per Protocol
PRO	patient-reported outcome
PT	Preferred Term
QTcF	Fridericia corrected QT interval
SAP	statistical analysis plan
SAE	serious adverse event
SD	standard deviation
SE	standard error
SOC	System Organ Class
SSR	sample size reestimation
TEAE	treatment-emergent adverse event
TFL	tables, figures, and listings
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
WHO	World Health Organization

1. Source Documents

The Statistical Analysis Plan (SAP) was written based on the following documentation:

Document	Date	Version
Protocol	05 December 2019	Final
Protocol Amendment	17 March 2020	1
Protocol Amendment	28 August 2020	2
Protocol Amendment	09 October 2020	2.0.1
Protocol Amendment	18 November 2020	3
Protocol Amendment	09 September 2021	4
eCRF	30 September 2020	3

2. Protocol Details

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of LX9211 in reducing pain related to diabetic peripheral neuropathy (DPN).

2.1.2 Secondary Objective(s)

The secondary objective of this study is to assess other effects and patient reported outcomes of LX9211 versus placebo following the 6-week double-blind Treatment Period.

2.1.3 Other Objective(s)

Other objectives of this study are:

- Change from Baseline in the Neuropathic Pain Symptom Inventory (NPSI) and to each week in the average daily pain score (ADPS), based on Question 5 of the Brief Pain Inventory – DPN (BPI-DPN).
- To evaluate plasma C_{trough} levels of LX9211 at 2 oral dose levels in patients with type 1 diabetes mellitus (T1DM) and/or type 2 diabetes mellitus (T2DM) with chronic diabetic peripheral neuropathy pain (DPNP) over a 6-week period.

The full pharmacokinetic (PK) profile of LX9211 will be evaluated in an optional substudy conducted in patients who consent to intensive PK sampling over the course of the treatment period.

Safety will be assessed by adverse events (AEs), vital signs, electrocardiogram (ECG) findings, and laboratory parameters.

2.2 Overall Study Design

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in patients with DPNP. Up to 282 patients are expected to enroll in this study.

Scheduled study visits in the clinic will occur during Screening; at the initiation of the 2-week single-blind placebo Run-in Period; on Day 1 (Baseline) and during Weeks 2, 4, and 6 of the double-blind Treatment Period, and Week 11 of the single-blind Safety Follow-up Period.

Male and female patients of age 18 years and above, diagnosed with T1DM or T2DM and with chronic DPNP, and who meet all inclusion and no exclusion criteria are eligible for enrollment.

Eligible patients may continue use of 1 medication prescribed for DPNP including pregabalin, gabapentin, and antidepressant medications, as long as they have been at stable doses for at least 1 month prior to screening and are willing to maintain their doses for the duration of the study. Use of any opioid medications for the management of DPNP within the 2 months prior to Screening is not permitted.

Screening Period: After signing the Informed Consent Form (ICF), all patients will enter a Screening Period of up to 2 weeks. Following confirmation of eligibility criteria, patients will enter the following study periods:

Run-in Period: After meeting Screening eligibility criteria, patients will enter a 2-week single-blind Run-in Period. On Day 1 of the Run-in period, patients will be administered 4 tablets of single blind study drug at the site. For the remainder of the Run-in Period, patients will take a single tablet of study drug in the morning. Each evening patients will rate and record the intensity of their DPNP over the previous 24 hours based on Question 5 of the BPI-DPN by answering the question "Please rate your pain due to your diabetes by indicating the one number that best describes your pain on the average." (0 [no pain] to 10 [pain as bad as you can imagine]) in their daily pain diary and will rate the interference of pain with sleep by completing Question 9F of the BPI-DPN. The ADPS will be calculated using all available daily pain diary data. In order to qualify for randomization, patients must

complete ≥70% of the daily pain diary entries during the week prior to randomization, meet criteria for moderate to severe pain, and demonstrate ≥80% compliance with taking the expected amount of placebo tablets during the Run-in Period. During the Run-in Period patients will not be allowed to use any rescue medication. On the morning of the Run-in Visit, patients may consume a light meal prior to the visit.

Note: Patients who fail Screening may be rescreened ONCE after discussion with the Medical Monitor.

Randomization/Double-blind Treatment Period: Patients who successfully complete the 2-week single-blind placebo Run-in Period and meet all other eligibility criteria will enter a 6-week double-blind Treatment Period.

Patients will be randomly assigned in a 1:1:1 ratio among the following 3 treatment groups:

- **Group 1:** LX9211 100 mg* / 10 mg**, once daily (qd)
- **Group 2:** LX9211 200 mg* / 20 mg**, qd
- **Group 3:** Placebo, qd

* Loading dose (Day 1)
** Maintenance dose (Day 2 – Week 6 Visit)

Implementation of the treatment randomization schedule will be centralized. A 1:1:1 ratio for assigning patients among the treatment groups will be accomplished by use of randomly permuted blocks of fixed size.

On Day 1, patients will receive 1 of 2 dose levels of LX9211 or placebo, based on their treatment assignment, to be given as a loading dose at the clinic. Patients will remain at the clinic for observation for 2 hours following dosing. At 2 hours ± 10 minutes, orthostatic vital signs will be obtained (heart rate and blood pressure) after which time patients may be released. The loading dose will be followed by a daily maintenance dose taken at home on Day 2 through the Week 6 Visit. **Note:** On days of the clinic visits, patients will refrain from taking their daily dose until after the visit.

Each evening during the double-blind Treatment Period, patients will be required to rate and record the severity of their DPNP over the previous 24 hours based on Question 5 of the BPI-DPN by answering the question "Please rate your pain due to your diabetes by indicating the one number that best describes your pain on the average." (0 [no pain] to 10 [pain as bad as you can imagine]), record the use of rescue medication (acetaminophen), and rate the interference of the patient's pain with sleep based on Question 9F of the BPI-DPN. The ADPS will be calculated using

all available data, however a minimum of 4 days (consecutive or non-consecutive) from the last week prior to each clinic visit is required for the calculation of weekly averages.

On the day of randomization, patients will also receive a bottle of acetaminophen. If a patient is unable to tolerate their DPNP, they are encouraged to discuss treatment options with the Investigator. At the Investigator's direction, the patient may be permitted to take acetaminophen (up to a maximum of 3 grams per day) as a rescue medication. If rescue medication does not provide adequate pain relief, the patient may discontinue from further participation in the study after consultation with the Investigator. Patients discontinuing the study prior to completion of the Week 6 Visit should also complete the Safety Follow-up Visit 5 weeks later.

Safety Follow-up Period: Following completion of the 6-week double-blind Treatment Period, all patients will enter the 5-week single-blind Safety Follow-up Period and take 1 tablet of single-blind study drug each morning during this period. During the 5-week single-blind Safety Follow-up Period, patients are allowed use of rescue medication (acetaminophen) if needed. Each evening patients will continue to rate and record the average severity of their DPNP over the previous 24 hours using Question 5 of the BPI-DPN and record the use of rescue medication (acetaminophen).

Blood samples for the determination of plasma LX9211 trough levels (C_{trough}) will be collected predose on Day 1, and at Weeks 2, 4, and 6 clinic visits, just prior to the dosing of study drug on the day of the visit. At the Week 11 EOT/EW Visit, a final sample will be collected.

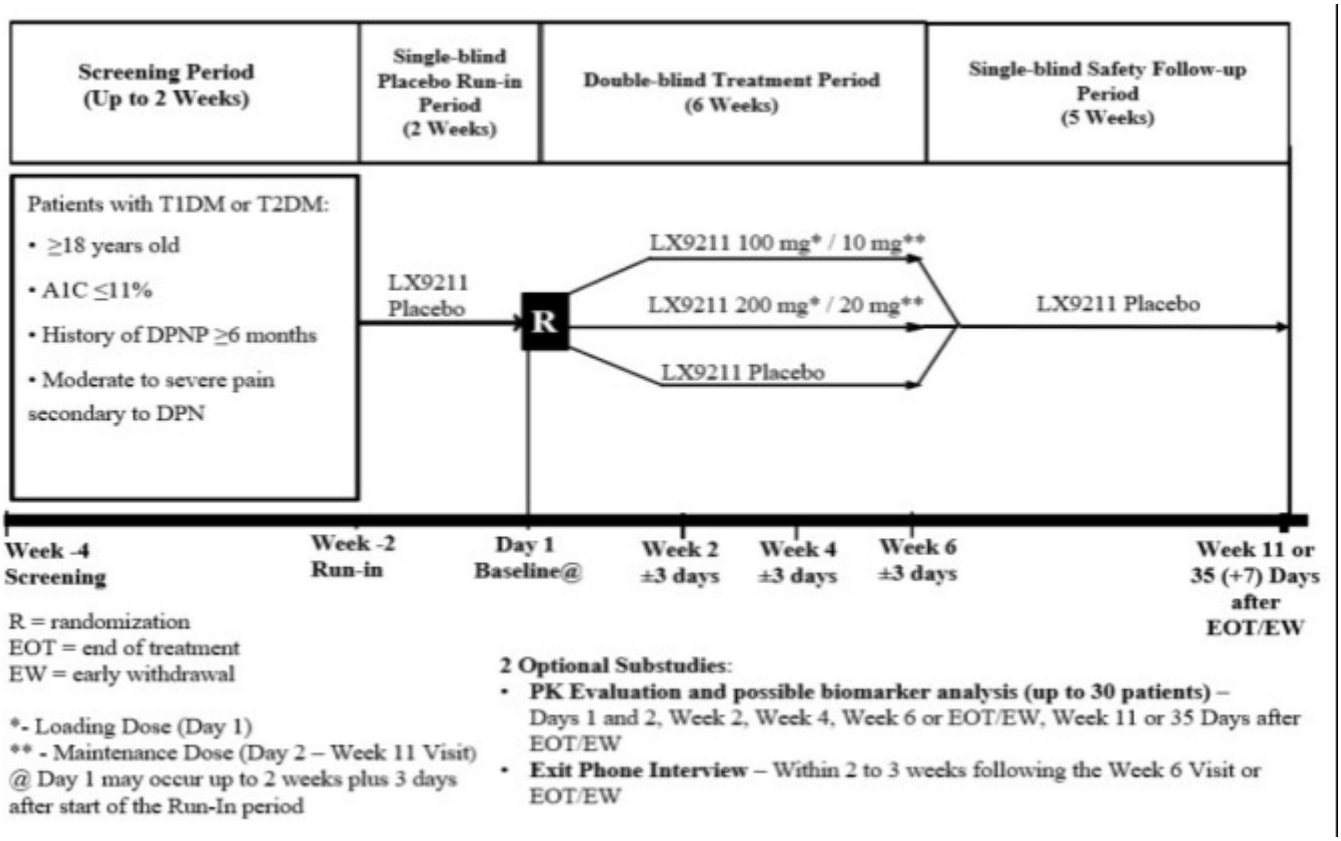
Optional Substudies: During the Screening Visit, patients may choose to participate in 1 or both of 2 optional substudies.

The first substudy will include approximately 30 patients for intensive blood sampling for determination of LX9211 plasma concentrations to allow for PK parameter estimation, and additional samples for possible biomarker analyses. The PK intensive sampling will occur on Days 1 and 2 and at the Week 6 clinic visit. These patients will be confined to a clinical research unit (CRU) twice during the study for intensive PK evaluation and biomarker evaluation: prior to and following the first dose of study drug and prior to and following their final dose of study drug (planned for Week 6).

The second optional substudy is a qualitative patient interview, which will include 60 to 85 patients. The interview will be conducted over the telephone and is designed to gain insight and understanding of patients' experiences with symptoms

of DPNP and to assess the relevance and clinical meaningfulness of symptom improvements (eg, reduction in pain) with LX9211 treatment.

The study design is presented in the diagram below:



2.3 Sample Size and Power

A sample size of 75 patients per treatment group who complete the 6-week double-blind Treatment Period will yield 80% power to detect a true mean difference of 1 unit between at least 1 of LX9211 treatment groups and placebo in ADPS change from Baseline, assuming a common standard deviation of 2 and an overall significance level of α=0.05 (2-sided Dunnett's test). Accounting for a dropout rate of 20%, a total of 282 patients (94 patients per treatment group; 75 patients x 1/(1-0.20)) will be enrolled and randomly assigned to treatment in a 1:1:1 ratio. This sample size is adjusted for the multiple comparisons of each LX9211 treatment group with placebo (Westfall, 1999).

Sample Size Reestimation

Due to the uncertainty in the outcome for the primary endpoint analysis secondary to potential variations in some of the key design parameters such as the dropout rate and standard deviation associated with the targeted treatment group

difference, an unblinded SSR adaptation will be implemented at the time of the interim analysis testing for futility. This will occur when the first 141 patients have been accrued and followed thru Week 6 or dropped out early from the trial (whichever event happens first). Should a patient drop out early in the study, but return for the Week 6 visit, the Week 6 data will be used in the analysis. The Chen-DeMets-Lan method will be used for the unblinded SSR since it requires minimal change from a group sequential test. This method requires specification for a number of criteria related to the allowable conditions for increasing the sample size that ensures that ordinary group sequential methods can be applied while seeing that the overall error is not inflated compared to the original group sequential design. The two primary conditions which are required and satisfied in the SSR for this study are that (a) the SSR is made at the penultimate look, and (b) the conditional power at the penultimate look occurs between 50% and 80.3% (the original specified power under the group sequential design). The SSR is linked to the projected effect size falling within this "promising" or "favorable" range of conditional power. Having satisfied these 2 main conditions, the Type I error rate after increasing the sample size until the conditional power equals the original target power will not be greater than the Type I error from the originally proposed design.

To derive the reestimated number of patients at the interim analysis, a simulation will be made that inputs: the observed group mean difference and its common standard deviation, a value for the maximum total number of patients (E[Max]) equal to 351 patients and, specification that the reestimation rule is the Exact E method. The Exact E method increases the patient number total until the desired conditional power is achieved.

nQuery Advisor Advanced Pro software (v8.5.2.0) (Statsols, Rathmaculling West, Cork, Ireland) was used to estimate the sample sizes.

3. Efficacy and Safety Variables

3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from Baseline (Week 2 of the Run-in Period) to Week 6 in ADPS, based on Question 5 of the Brief Pain Inventory - DPN (BPI-DPN), the 11-point scale (0 [no pain] to 10 [pain as bad as you can imagine]).

3.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are to be assessed in each LX9211 dose group versus placebo comparison for each of the following variables listed below:

- Proportion of patients with ≥30% reduction in pain intensity in ADPS based on Question 5 of the Brief Pain Inventory - DPN (BPI-DPN) from Baseline to Week 6
- Proportion of patients with ≥50% reduction in pain intensity in ADPS based on Question 5 of the Brief Pain Inventory - DPN (BPI-DPN) from Baseline to Week 6
- Change from Baseline to Week 6 in the severity of pain and interference of pain with sleep and other aspects of the patient's life based on the Brief Pain Inventory (BPI) Short Form for diabetic peripheral neuropathy (BPI-DPN) including the following:
  - Pain at its worst
  - Pain at its least
  - Pain right now
  - Interference score averaged over Questions 9A-G
  - General activity
  - Mood
  - Walking ability
  - Normal work
  - Relations with other people
  - Sleep
  - Enjoyment of life
- Proportion of patients discontinuing treatment due to lack of efficacy defined as increase in ADPS based on Question 5 of the Brief Pain Inventory - DPN (BPI-DPN) from Baseline of 30%
- Patient Global Impression of Change (PGIC) at Week 6
- Time to loss of efficacy from Week 6 to Week 11 among patients achieving at least 30% reduction in pain intensity in ADPS based on Question 5 of the Brief Pain Inventory - DPN (BPI-DPN) at Week 6

3.3 Other Efficacy Endpoints

The other efficacy endpoints are to be assessed in each LX9211 dose group versus placebo comparison for each of the following variables listed below:

- Change from Baseline to Week 6 in the NPSI
- Change from Baseline to each week in ADPS, based on Question 5 of the BPI-DPN
- Proportion of patients with ≥30% reduction from Baseline, based on Question 5 of the BPI-DPN by week
- Proportion of patients with ≥50% reduction from Baseline, based on Question 5 of the BPI-DPN by week

- Cumulative percentage of percent change in ADPS based on Question 5 of the BPI-DPN from Baseline to Week 6 comparing each LX9211 treatment group to placebo
- Cumulative percentage of percent change in ADPS based on Question 5 of the BPI-DPN from Week 6 to Week 11 comparing each LX9211 treatment group to placebo

3.4 Safety Variables

Safety endpoints are as follows:

- Incidence of treatment-emergent adverse events (TEAEs), suspected adverse reaction, AEs leading to discontinuation from the study, serious adverse events (SAEs), and deaths
- Actual and change from Baseline in clinical laboratory results
- Actual and change from Baseline in vital signs results, including weight
- Clinically significant change from Baseline in physical examination (PE) findings
- Actual and change from Baseline in ECG findings

4. Pharmacokinetic (PK) Variables

PK endpoints from the optional PK substudy may include, but are not limited to:

- $AUC_{0\text{-}24}$
- $AUC_{0\text{-}tlast}$
- $AUC_{0-\infty}$
- $AUC_{0\text{-}\tau}$
- CL/F
- CL/F/kg
- C_{max}
- C_{ss}
- t_{max}
- $t_{1/2}$
- Vz/F
- λz

Biomarker samples will be collected for patients participating in the PK substudy.

5. Analysis Populations

Analysis of the primary and secondary efficacy endpoints will be based on the Modified Intent-to-Treat (mITT) population. Safety endpoints analyses will be based on the Safety population.

5.1 Intent-to-Treat (ITT) Population

The ITT population will include all randomized patients.

5.2 Modified Intent-to-treat (mITT) Population

The mITT population will include all randomized patients who take at least 1 dose of study drug. mITT patients will be analyzed according to their randomized treatment.

5.3 Per Protocol (PP) Population

The PP population will include patients in the mITT population who complete treatment through the primary assessment of the first 6 weeks, and did not have any important protocol deviations that would interfere with the collection or interpretation of the efficacy data.

Protocol deviations are defined as any change, divergence, or departure from the study design or procedures defined in the study protocol. Important protocol deviations are a subset of protocol deviations and may significantly impact the correctness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. Section 5.3.1 details the types of deviations.

5.3.1 Important Protocol Deviations Leading to Exclusion from the PP Population Analysis

Only those important protocol deviations considered to have a major effect on efficacy will lead to complete exclusion of the patient from the PP population. For the purposes of this study, the following criteria have been identified as important protocol deviations leading to exclusion from the PP population as it is considered that the occurrences of any of these criteria might have an important influence on the primary efficacy endpoint.

Type	Important Protocol Deviation Leading to Exclusion from the PP population	Method of Identification
Prohibited Medication	Patients who take medications that are not permitted during the double-blind Treatment Period	**Non-programmable** review of blinded prior and concomitant medications listings Labcorp will provide the Medical Monitor with the lists of prior and concomitant medications taken by patients. The Medical Monitor will review this list and note any prohibited medications or therapies within 1 month prior to the Screening Visit. Patients will be excluded if they had prohibited medications or therapies within 1 month prior to the Screening Visit.
Entry Criteria Violations	Patients did not meet Inclusion Criterion 9 which is thought to impact efficacy	**Programmatic** check based on eligibility data
Noncompliance During 6-week Double-blind Treatment Period	Patients who had low study drug compliance rate (<80%)	**Programmatic** check based on exposure and drug accountability data
Minimum Treatment Duration	Patients did not receive at least 5 weeks of double-blind treatment	**Programmatic** check based on the exposure data
Week 6 ADPS Missing	Patients did not have at least 4 ADPS scores within Week 6 in order to calculate weekly ADPS	**Programmatic** check of ADPS data
Errors in Treatment Allocation	Patients who received a wrong treatment at 1 or more study visits due to packaging or dispensing errors during the double-blind Treatment Period	**Programmatic** check based on unblinded IRT database after the study is unblinded. The check will be done by comparing the kit number that IRT had assigned to the patient/visit against the kit number actually used.

Incorrect Stratum used in Randomization	Patients were randomized using an incorrect stratum	**Programmatic** check of IRT database compared to ADPS from Run-in
Clinical Trial Management System	Labcorp Clinical will provide the list of protocol deviations based on the clinical monitoring.	**Non-programmable:** The list will be reviewed prior to database lock and unblinding, and the important protocol deviations leading to exclusion from the PP population will be identified.

As defined in the table, a set of the important protocol deviations leading to exclusion from the PP population will be determined programmatically from the data. Those criteria which require clinical or medical monitoring interpretation will be reviewed prior to database lock.

All important protocol deviations occurring during the study will be reviewed and approved by Lexicon Pharmaceuticals, prior to database lock unblinding. Should additional important protocol deviations leading to exclusion from the PP population, not anticipated at the time of preparing this SAP, be identified during the study (and prior to unblinding), they will be provided in a separate document and included in all relevant protocol deviation reviews and approvals.

5.4 PK Populations

There are 2 PK populations as defined below.

5.4.1 PK Population - C_{trough}

The PK population for evaluation of C_{trough} will include all patients who receive at least 1 dose of study drug and have at least 1 C_{trough} sample collected.

5.4.2 PK Population - Substudy

The PK population for the PK Substudy will include patients who receive at least 1 dose of study drug and who have a predose sample and have at least the minimum of samples required to estimate the PK parameters.

5.5 Safety Population

The Safety population is defined as those randomized patients who take at least 1 dose of study drug during the double-blind Treatment Period. Safety patients are analyzed according to their actual treatment received on Study Day 1.

6. Data Handling

6.1 Time Points and Visit Windows

Day 1 is defined as Baseline/Randomization visit, is also the first day that study treatment during the double-blind Treatment Period is planned to be started. Should study treatment start at a later date, Day 1 will be defined as the date that study treatment during the double-blind Treatment Period is initiated. Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1; there is no Day 0.

6.1.1 Primary efficacy, secondary efficacy, and other efficacy endpoints based on daily pain diary data

The following visit windows defined in Table 1.1 will be used for the analyses of the primary efficacy endpoint, the secondary efficacy and other efficacy endpoints based on the ADPS as well as for the secondary endpoint on pain interfering with sleep.

Table 1.1 Definition of time point windows for analyses based on ADPS and sleep interference rated each evening

Time point	Time point window [a]
Baseline	Day -7 to Day -1
Week 1	Days 1 to 7
Week 2	Days 8 to 14
Week 3	Days 15 to 21
Week 4	Days 22 to 28
Week 5	Days 29 to 35
Week 6	Days 36 to 42
Week 7	Days 43 to 49
Week 8	Days 50 to 56
Week 9	Days 57 to 63
Week 10	Days 64 to 70
Week 11	Days 71 to 77

[a] relative to the date of first dose of study drug during the double-blind Treatment Period/date of Randomization/date of Baseline Visit (Day 1)

The Baseline value for ADPS based on Question 5 of the BPI-DPN will be calculated as the mean value of the corresponding question over Week 2 of the single-blind Run-in Period, provided that ≥5 days with non-missing data from that period are available for analysis. The Baseline value for the interference with sleep using Question 9F of the BPI-DPN will be calculated as the mean value of the

corresponding question over Week 2 of the single-blind Run-in Period, provided that ≥5 days with non-missing data from that period are available for analysis.

The post-Baseline values will be calculated as the mean value of the corresponding question, ie, Question 5 for ADPS and Question 9F for interference with sleep of the BPI-DPN, rated by patients each evening in the daily pain diary and collected during the target week period. A minimum of 4 non-missing data points within the target week period is required for the calculation of the mean value for that particular week.

6.1.2 Secondary efficacy and other efficacy endpoints based on data collected at clinic visits

The rest of the efficacy endpoints based on data collected at clinic visits will follow the visit windows defined in Table 1.2.

Table 1.2 Definition of visit windows for efficacy data collected at each visit

Visit	Target Day of Visit[a]	Acceptable visit window
Screening	Day –28	NA
Run-in [b]	Day –14	NA
Baseline	Day 1	Day 1 to Day 4
Week 2	Day 15	Day 5 to Day 22
Week 4	Day 29	Day 23 to Day 36
Week 6	Day 43	Day 37 to Day 60
Week 11	Day 78	Day 61 to 35 days after the last treatment dose during the double-blind Treatment Period

[a] relative to the date of first dose of study drug during the double-blind Treatment Period/date of Randomization/date of Baseline Visit (Day 1)
[b] weight is collected

In general, the Baseline value for a variable is defined the last value collected or taken on or before Day 1 and prior to the first dose of double-blind study drug. In cases where there are multiple such values, the non-missing value closest to the start of study treatment is selected. If time is available for an assessment on Day 1, it will be compared with dosing time on Day 1 to define the Baseline value.

Multiple visits within the same window will be dealt with as follows:

- If both scheduled and unscheduled visits fall within the same visit window, the scheduled visit will be used for analysis.
- If multiple scheduled visits occur within a single visit window, then the visit closest to the target day of the visit window will be used in the analysis. If there is a tie, the later visit will be used in the analysis.

- If multiple unscheduled visits occur within a single visit window (with no scheduled visit within the window) then the unscheduled visit closest to the target day of the visit window will be used in the analysis. If there is a tie, the later unscheduled visit will be used in the analysis.

6.1.3 Safety analyses

Safety analyses for the laboratory assessments, vital signs, ECG and physical exam data will use the study visit window rules used to assign observations to visits as defined above in Table 1.2.

6.2 Handling of Dropouts, Missing Data, and Outliers

Missing data will not be imputed for safety analyses. The safety evaluations will be performed on observed data only.

For AEs with partial or missing onset or stop dates:

AE stop date will be imputed first as:

- If stop date is completely missing, assume it is ongoing (no imputation);
- For a partial AE stop date:
  - day is missing, then take the last day of the month
  - both day and month are missing, then take the last day of the last month that the patient was on study

Then AE onset date will be imputed as:

- If onset date is completely missing: the first dose date
- For a partial AE onset date:
  - day is missing:
    - Partial date < the first dose date: last day of the month
    - Partial date = the first dose date: the first dose date
    - Partial date > the first dose date: first day of the month
  - both day and month are missing ie only the year is available:
    - Partial date < the first dose date: December 31st
    - Partial date = the first dose date: the first dose date
    - Partial date > the first dose date: January 1st

If the imputed AE onset date is after the AE stop date/imputed AE stop date, then the onset date will be set to the AE stop date/imputed AE stop date.

The imputed dates will not be listed. Study day relative to the first dose of double-blind study drug associated with missing or partial dates will not be displayed in AE listings.

In the event that a partial date (month/year or year) for concomitant medication is available, this information will be used as follows:

- When both month and year are available – first day of the month will be used for start date and the last day of the month will be used for the stop date.
- When only year is available – January 1st will be used for the start date and December 31st will be used for the stop date.

The imputed dates will only be used to determine whether a concomitant medication will be classified as prior medication or concomitant medication.

For patients who complete the NPSI assessment, but have 1 incomplete answered question, the total score will be computed as 10 times sum of scores of 9 descriptors divided by 9. If more than 1 question is missing, then the total score will be missing. Missing questions will not be imputed for the subscores.

For patients who complete the BPI-DPN assessment Questions 9A-G and have less than 4 missing questions, the Interference score averaged Questions 9A-G will be computed as the mean of the answered questions. If 4 or more questions are missing, then the Interference score will be set to missing.

The Hospital Anxiety and Depression Scale (HADS) is collected only at Screening and imputation of missing data are not critical for this assessment.

No rules for outlier detection are planned.

6.2.1 Observed Cases Datasets

The mixed-effects model for repeated measurements (MMRM) will be performed based on a missing at random (MAR) assumption using data actually observed - observed cases (OC) dataset. The OC datasets will be used for analysis of the primary efficacy as well as all secondary efficacy and other efficacy endpoints. This dataset will not impute any values for missing observations, unless mentioned otherwise.

6.2.2 Pattern-mixture Model

As a sensible sensitivity analysis to the MMRM, a method for missing value imputation based on pattern-mixture model (PMM) will be used to analyze the data under the assumption that the data is missing not at random (MNAR): missingness depends on the unobserved values and cannot be predicted solely based on a patient's observed data. It is assumed that the great majority of missing data are caused by patients discontinuing prior to the study visit at which primary endpoint data are collected and the resulting missing data will have a monotone pattern. There may also be some small amount of non-monotone missing data when patients skip intermediate visits but return for evaluations at subsequent visits.

Methods will be adopted to estimate for both non-monotone and monotone missing data patterns. The PMM analysis will serve as the primary sensitivity analysis of the primary efficacy endpoint (see Section 7.6.3 for more details).

7. Statistical Methods

7.1 General Principles

All data processing, summarization and analyses will be performed using Hosted SAS Environment / Version 9.4 (or later) of the SAS® (SAS Institute, Cary, NC) statistical software package.

The following principles will be applied to all tables, figures, and listings (TFLs) unless otherwise stated:

Principle	Value
Significant tests	2-sided and use a 5% significance level for the main effect of study treatment
Treatment group labels and order presented	Placebo LX9211 100 mg/10 mg LX9211 200 mg/20 mg Total (if applicable)
Tables	Data in summary tables presented by study drug group, assessment (where applicable) and visit (where applicable)
Listings	All data collected presented by study drug group, center, patient, and visit (where applicable), date, unless otherwise specified
Descriptive summary statistics for continuous variables	Number of patients/observations with non-missing data (n), mean, standard deviation (SD), median, minimum and maximum. If n=0 then other statistics will be blank.
Descriptive summary statistics for categorical variables	Frequency counts and associated percentages [n (%)] presented to 1 decimal place.
Denominator for percentages	Number of patients in the analysis population, unless stated otherwise in table shell(s)
Include "Missing" as category	Yes, when the number missing is greater than 0 for at least 1 treatment group
Display for 0 percentages	Leave Blank
Display for treatment compliance and percentage change from Baseline	Present mean and median to 1 decimal place and SD to 2 decimal places
Display to 1 more decimal place than collected value	Mean Mean Difference Median Confidence Interval

Principle	Value
Display to 2 more decimal places than collected value	SD Standard Error
Display for p-values	x.xx for p-value>0.05 x.xxx for p-value≤ 0.05 and ≥0.001 <0.001 for p-value<0.001
Limit of precision for displays	3 decimal places
Date Format	DDMMMYYYY
Display for analysis not done	NC (not calculated), NA (not applicable), ND (not done), or NR (not reported). Refer to table shells.

For continuous efficacy variables that are derived as percentage change from Baseline outcomes, the applied analyses and their results will be used for descriptive purposes.

Analysis and summarization of treatment group comparisons for the safety endpoints will be reported in their original measurement units and converted values to accommodate regulatory review by the Food and Drug Administration and external authorities, where appropriate.

All significance tests will be 2-sided and use a 0.05 α-level unless specified otherwise.

7.2 Patient Disposition and Data Sets Analyzed

Patient disposition will be listed and summarized by treatment group and overall, and will include the number and percentage of patients:

- Screened
- Entered single-blind placebo Run-in Period
- Discontinued single-blind placebo Run-in Period
- Randomized
- Randomized and not treated
- Treated
- Completed double-blind Treatment Period
- Discontinued double-blind Treatment Period
- Entered optional PK substudy
- Entered optional qualitative patient interview substudy
- Completed single-blind placebo Safety Follow-up Period
- Discontinued single-blind placebo Safety Follow-up Period

- Included in each study population (ITT, mITT, PP, PK – Substudy, PK - C_{trough} and Safety)

The number and percentage of patients who complete the study and who discontinue early (including a breakdown of the primary reasons for discontinuation), will be presented for the ITT population. In addition, the number of patients who discontinue from the double-blind Treatment Period and single-blind Safety Follow-up Period will be summarized by treatment group, respectively.

A summary of patient enrollment by site will also be provided by treatment group and overall for the ITT population. A summary of patient enrollment by randomization strata of baseline pain severity (moderate or severe pain, based on ADPS) will also be provided by treatment group, respectively.

Randomization strata will be collected in the Interactive Voice/Web Response System (IXRS) and it is defined as the average of the scores recorded in the pain diary, ie, Question 5 of the BPI-DPN, during the 2-week single-blind Run-in Period. The rounded average score will be classified as below:

- Moderate: [5-7]
- Severe: [8-9]

A summary of the reasons for screen failure as well as the number of patients screened but not randomized will be produced. No other information for screen failures will be presented.

7.3 Protocol Deviations

All-important protocol deviations leading to exclusion from the PP population (see Section 5.3.1) will be listed and summarized by study drug group for the mITT population.

The deviations will be identified before data are unblinded.

7.4 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be listed and summarized by treatment group and overall for the mITT population. Standard descriptive statistics will be presented for the continuous variables of:

- Age at time of Informed Consent (years)
- Weight (kg), to convert pounds (lbs) to kilograms, multiply the pound value by 0.45359237
- Height (cm), to convert inches (in) to centimeters, multiply the inches value by 2.54

- Body mass index (BMI) (kg/m^2)
- Sitting systolic blood pressure (BP) (mm Hg)
- Sitting diastolic BP (mm Hg)
- Pulse rate (beats per minute [bpm])
- Respiration rate (breaths/min)
- Temperature (C), to convert Fahrenheit (F) to Celsius, (Fahrenheit value (F) – 32) * 5/9
- HADS-Depression and HADS-Anxiety subscores

The total counts and percentages of patients will be presented for the categorical variables of:

- Age at time of Informed Consent (grouped as <75 years, ≥ 75 years)
- Sex
- Race
- Ethnicity
- Fertility status (females only)
- Method of contraception
- Baseline pain severity categorized by randomization strata (as derived using average pain scores collected during the 14-day Run in data)
- Baseline ADPS (as derived using week 2 of Run-in data)
- DPNP drug use (Yes, No)

A summary of Baseline physical examination data will be presented by treatment group and overall for the mITT population.

Other baseline measurements, such as laboratory evaluations and ECG, will be summarized by treatment group with the post-Baseline measurements.

No formal tests of statistical significance will be performed on the demographic and Baseline characteristics data.

7.4.1 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [Version 23 (or a later version if updated during the study)]. All medical history will be listed, and the number and percentage of patients with any medical history will be summarized for the mITT population by System Organ Class (SOC) and Preferred Term (PT) for each treatment group and overall.

7.4.2 Prior and Concomitant Medications

Medications received prior to or concomitantly with study drug will be coded using the World Health Organization (WHO) Drug Dictionary [Version B3 Sep2020 (or a later version if updated during the study)], Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications and concomitant medications are defined as follows:

- Prior medications are those taken prior to the first dose date of double-blind treatment, and have a stop date before first dose date of double-blind treatment.
- Concomitant medications are those with a start date on or after the first dose date of double-blind treatment, or those with a start date before the first dose date of double-blind treatment and a stop date on or after the first dose date of double-blind treatment.

If a medication cannot be classified as "prior" or "concomitant" after applying imputation rules for missing/incomplete dates, it will be classified as concomitant.

Prior medications, concomitant medications taken during double-blind Treatment Period (excluding prohibited and rescue concomitant medications), prohibited concomitant medications taken during double-blind Treatment Period, and concomitant medications started during Safety Follow-up Period (those medications starting after the last dose of double-blind study drug and through the end of the patient's Safety Follow-up Period) will be summarized separately by treatment group and overall for the mITT population.

The number and percentage of patients using each medication will be displayed together with the number and percentage of patients using at least 1 medication within each therapeutic class (ATC-Level 2), chemical subgroup (ATC-Level 4), and generic term.

The percentage of patients who need rescue medication during the double-blind Treatment Period will be summarized descriptively by treatment group and overall for the mITT population.

Prior medications, concomitant medications and rescue concomitant medications will be listed separately.

7.5 Measurements of Treatment Compliance

Percentage compliance in the double-blind Treatment Period will be calculated as:

(number of actual tablets taken) * 100 / Number of tablets expected to be taken

Where actual tablets taken will be defined as the total number of tablets dispensed minus the total number of tablets returned during the double-blind Treatment Period. The number of tablets expected to be taken will be defined as the number of days within the double-blind Treatment Period.

Percentage compliance will be summarized descriptively by treatment group and overall for the Safety population.

The number and percentage of compliant patients will be presented by treatment group and overall for the Safety population, where compliant is defined as percentage compliance between 80.0% and 100.0% inclusive. The following percentage compliance categories will also be presented:

- <80.0%
- 80.0-100.0%
- >100.0%

7.6 Efficacy

The 6-week double-blind Treatment Period will provide the main dataset for inferential analyses.

All efficacy analyses will be performed on the mITT population. Supportive analyses will be performed on the PP population.

The 2 pairwise comparisons of each LX9211 dose levels vs placebo will be performed using Dunnett's test. Testing among the secondary endpoints will not be adjusted for multiplicity, and hence, the analyses will be exploratory. Other endpoints will likewise not be adjusted for multiple testing. Adjusted and unadjusted p-values will be presented.

7.6.1 Primary Efficacy Analysis

The primary endpoint is the change from Baseline to Week 6 in ADPS, based on Question 5 of the BPI-DPN, the 11-point scale (0 [no pain] to 10 [pain as bad as you can imagine]). The primary analysis will be based on observed data including data measured after the initiation of rescue medications.

Baseline is defined as the average of the Week 2 Run-in Period data collected by patients in the daily pain diary, provided that ≥5 days from that period are available for analysis. The post-Baseline values will be calculated by week as the mean value of the Question 5 for ADPS of the BPI-DPN, rated by patients each evening and collected during the target week period. A minimum of 4 non-missing data within the target week period is required for the calculation. The change from

Baseline values at post-Baseline weeks will be calculated as the absolute difference between the Baseline value and post-Baseline values, ie

change from Baseline = post-Baseline value – Baseline value

The ADPS calculated for each post-Baseline week until Week 6, and the change from Baseline in ADPS at post-Baseline weeks until Week 6 will be summarized by Week using standard descriptive statistics. Data from all study visits, scheduled and unscheduled, and from the daily pain diary will be listed.

A restricted maximum likelihood-based, MMRM approach will be used to assess the difference between LX9211 and placebo in the primary endpoint (ie, change from Baseline to Week 6 in the ADPS derived from data collected daily from Question 5 of the BPI-DPN instrument). The MMRM model will include fixed effects of treatment, week, treatment-by-week interaction, the randomization stratum of Baseline pain severity (moderate, severe), and Baseline ADPS score as a covariate. An unstructured covariance structure will be used to model the within-patient error. Other covariance structures will be explored should convergence not be met. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom.

The adjusted mean change in ADPS from baseline to Week 6 for each treatment group and the 95% confidence intervals (CIs) will be estimated in the framework of this model, as well as the between-group differences (comparing each LX9211 treatment group to placebo) and the 95% CIs for the difference.

Summarization of the inferential statistics will include the Least Squares means (LS means), standard error (SE) of the estimates, p-values, and 2-sided 95% CIs. These statistics will be provided for the within treatment group changes from Baseline and for the comparison of each dose level of LX9211 (100 mg/10 mg or 200 mg/20 mg) versus placebo for the change from Baseline scores. Tabulation of the inferential results (CIs and p-values) will include the observed finds from the statistical model.

The same analysis will be performed using the PP population.

Figures displaying the arithmetic mean change from Baseline in ADPS by week as well as LS mean change by week, including Week 6, will be presented by treatment group for the mITT population.

7.6.2 Secondary Efficacy Analysis

Analysis of the secondary efficacy endpoints will be based on the mITT population. Descriptive statistics for all the secondary efficacy endpoints will be presented by treatment group and by study visit/week where appropriate. Data from all study

visits, scheduled and unscheduled, and from the daily pain diary will be listed. Post-Baseline data through Week 6 will be used in the analyses where inferential statistics are presented, including observations occurring after discontinuation of study drug. Figures displaying mean change from Baseline, LS mean change at Week 6, and bar charts displaying proportions, will be presented by treatment group.

Continuous secondary efficacy endpoints: BPI-DPN scores, measured at multiple time points, will be analyzed using a similar modeling strategy as for the primary endpoint.

The ordinal secondary endpoint, PGIC response at Week 6, will be analyzed using an analysis of variance (ANOVA) model to test and estimate the treatment effect.

Categorical secondary endpoints: the proportion of responders based on Question 5 of BPI-DPN and the proportion of patients discontinuing study treatment due to lack of efficacy will be compared between treatments using a Cochran-Mantel-Haenszel (CMH) test stratified by the randomization factor of Baseline pain severity (moderate, severe). Patients with missing measurement at Week 6 will be considered non-responders. In general, a non-responder imputation (NRI) rule will be applied to assign outcomes to all study weeks with missing observations.

The Kaplan-Meier (KM) method will be used to generate statistical summaries of the time to loss of efficacy variable among patients who achieve ≥30% reduction in ADPS based on Question 5 of the BPI-DPN from Week 6 to Week 11.

The qualitative patient interview substudy will be managed by a separate vendor (RTI-Health Solutions, Research Triangle Park, NC). The data analysis methods they employ will be detailed in a separate statistical analysis plan and the results will be reported separately by them.

7.6.2.1 Proportion of patients with ≥30% reduction in pain intensity in ADPS based on Question 5 of the BPI-DPN from Baseline to Week 6

Baseline and Week 6 ADPS scores will be based on the same mean values as derived for the primary endpoint. The frequency and percentage of patients with ≥30% reduction in pain intensity from Baseline at Week 6 will be presented by treatment group. Response/Non-response categories will be defined as:

- If % change from Baseline ≤ (-30) → Response
- If missing % change from Baseline or > (-30) → Non-response

Where % change from Baseline = 100*(post-Baseline value – Baseline value)/ Baseline value.

This endpoint will use a CMH test stratified by the different levels of the randomization stratification factors of Baseline severity score (moderate, severe). The treatment group comparisons of each dose level of LX9211 (100 mg/10 mg or 200 mg/20 mg) versus placebo will be performed at Week 6 only, with descriptive statistics provided for each week. 95% CIs for the difference between 2 proportions will be calculated using the asymptotic Wald method.

7.6.2.2 Proportion of patients with ≥50% reduction in pain intensity in ADPS based on Question 5 of the BPI-DPN from Baseline to Week 6

Baseline and Week 6 ADPS scores will be based on the same mean values as derived for the primary endpoint. The frequency and percentage of patients with ≥50% reduction in pain intensity from Baseline at Week 6 will be presented by treatment group. Response/Non-response categories will be defined as:

- If % change from Baseline ≤ (-50) → Response
- If missing % change from Baseline or > (-50) → Non-response

Similarly, this endpoint will be analyzed as for Section 7.6.2.1.

7.6.2.3 Change from Baseline to Week 6 in pain severity and pain interference based on questions from the BPI-DPN

The following pain severity and pain interference categories, completed at the time of the clinic visit (unless noted otherwise), will be analyzed separately:

- Pain at its worst
- Pain at its least
- Pain right now
- Interference score averaged over Questions 9A-G
- General activity
- Mood
- Walking ability
- Normal work
- Relations with other people
- Sleep
- Enjoyment of life

The interference score, averaged over Questions 9A-G, will be calculated as the mean of the 7 interference categories collected in Questions 9A-G during the clinical visits as long as at least 50% (ie, at least 4 of 7) of the scores are non-missing.

The change from Baseline to Week 6 in pain severity and pain interference will be summarized using standard descriptive statistics and the treatment effect will be evaluated using a similar MMRM method as specified for the primary efficacy analysis of change from Baseline to Week 6 in ADPS where the time point will be

substituted by Visit instead of Week. The Baseline covariate included in the model is the Baseline value of the dependent variable under analysis.

In addition, the change from Baseline to Week 6 in pain interference with sleep based on Question 9F, rated by patients and collected each evening in the daily pain diary will be summarized using standard descriptive statistics and the treatment effect will be evaluated using a similar MMRM method as specified for the primary efficacy analysis of change from Baseline to Week 6 in ADPS. In this case, the Baseline value for the interference with sleep using Question 9F of the BPI-DPN is defined as the value collected at the time of the clinic visit on Day 1. The post-Baseline values will be calculated by week as the mean value of the Question 9F of the BPI-DPN, rated by patients each evening and collected during the acceptable week period. A minimum of 4 non-missing data within the target week period is required for the calculation.

7.6.2.4 Proportion of patients discontinuing treatment due to lack of efficacy based on data collected for Question 5 of the BPI-DPN

This endpoint will be derived as follows:

1. Condition on the eCRF item if the patient stopped study treatment with reason of Lack of Efficacy.

2. If "Yes" to the above, calculate the % change from Baseline of ADPS based on Question 5 of the BPI-DPN during the double-blind Treatment Period, starting at Baseline and ending on the last assessment before the patient stopped study treatment. No minimum number of assessments is required.

3. If the derived value in #2 >= 30%, then the patient is classified as a "responder". If otherwise (including all mITT patients), then the patient is classified as a "non-responder".

Where % change from Baseline = 100*(last week of treatment value – Baseline value)/ Baseline value.

The frequency and percentage of patients discontinuing treatment during the double-blind Treatment Period due to lack of efficacy will be presented by treatment group. Similarly, this endpoint will be analyzed as described in for Section 7.6.2.1.

7.6.2.5 Patient Global Impression of Change (PGIC) at Week 6

The PGIC, a 7-point rating scale, will assess the patient's belief about their overall improvement experienced at the end of treatment.

The frequency and percentages of patients within each category at Week 6 will be presented by treatment group. The treatment effect will be evaluated using an

ANOVA model with treatment and randomization stratum of Baseline pain severity (moderate, severe) as independent variables. Least-square means of PGIC in each treatment group and the difference between LX9211 and placebo for each comparison, along with their 95% CIs and p-value will be presented.

7.6.2.6 Time to loss of efficacy from Week 6 to Week 11 among patients achieving ≥ 30% reduction in pain intensity in ADPS based on Question 5 of the BPI-DPN at Week 6

Time to loss of efficacy is defined as the time from the date of Week 6 visit to the date of termination of safety follow-up due to lack of efficacy. Termination of safety follow-up due to other reasons and death are competing risk. Patients who have terminated the safety follow-up due to any reason other than lack of efficacy after Week 6 visit or have completed the study through Week 11 will be censored at the date of the last ADPS assessment based on Question 5 of the BPI-DPN collected by patients in the daily pain dairy.

Time to loss of efficacy (weeks) = (date of termination of safety follow-up due to lack of efficacy or censoring – date of Week 6 visit + 1) / 7.

Only patients who achieved ≥30% reduction in pain intensity in ADPS based on Question 5 of the BPI-DPN from Baseline to Week 6 will be included in the analysis of time to loss of efficacy.

Kaplan-Meier estimates and the associated 95% CIs of the median, 25th, and 75th percentile will be presented. The 2-sided 95% CIs will be computed using the log-log transformation.

The minimum and maximum time to loss of efficacy (using censored and event times) will also be presented.

The survivor function will be displayed graphically by treatment group using a KM curve.

7.6.3 Sensitivity Analysis

In the event that rescue medication is used, a supplementary MMRM model will be applied to the primary endpoint dataset that excludes data collected after the initiation of the rescue medication using the mITT population. This model will be parameterized in the same manner as will be used for the primary analysis of this endpoint.

In addition, to assess the robustness of the MMRM analyses performed under the MAR assumption, and given the long half-life of LX9211, PMMs with copy reference-based imputation methods will be applied on both datasets (with and without data collected after the initiation of the rescue medication) using the mITT population.

Methods will be adopted to estimate for both non-monotone and monotone missing data patterns. Imputations for the non-monotone missing data pattern will be the initial step. The imputation algorithm based on Monte Carlo Markov Chain methodology will be used assuming a MAR mechanism for the missing data; 100 imputations will be used. Then multiple imputations will be performed to assign the response variable at consecutive study weeks in a sequential manner for the monotone missing data pattern. For this chain-based method, control-based imputation will be applied so that there is no direct use of observed data from the LX9211 treatment groups in estimating the imputation model. The method is derived such that it builds its imputation only on the placebo group data. The imputed datasets will be combined by use of Rubin's rule and analyzed using an analysis of covariance (ANCOVA) model fitted for the fixed effects of treatment, the randomization stratum of the Baseline pain severity (moderate, severe), and the continuous fixed covariate of Baseline score. The ANCOVA analysis will be performed at Week 6 only. Summary statistics from applying the ANCOVA model across the multiple imputed datasets will be combined to obtain an overall estimate of the treatment group differences.

Sensitivity analyses are not planned for analyses of the secondary or other efficacy endpoints.

7.6.4 Subgroup Analysis

The primary endpoint will be analyzed using the mITT population for the following subgroups:

- Baseline pain severity based on the actual stratum, moderate or severe
- Sex, male or female
- DPNP drug use, yes or no
- Subjects who experience the 5 specific TEAEs, yes or no

DPNP drug use subgroup is defined as those who took concomitant DPNP medications including the following: pregabalin, gabapentin, duloxetine, amitriptyline, venlafaxine, desvenlafaxine, valproic acid.

The 5 specific TEAEs refer to the AEs: dizziness, headache, nausea, somnolence, and balance disorder, which usually occur more frequently than other AEs.

The same MMRM covariates used for the primary endpoint analysis will be used for the subgroup analyses except that for the Baseline pain severity subgroup analysis, the randomization stratum of Baseline pain severity (moderate, severe) will not be included as a covariate. A forest plot of the LS Means difference and 95% CI for the

comparison of LX9211 versus placebo with the change from Baseline scores will be presented for all subgroups.

All subgroup analyses will be exploratory.

7.6.5 Other Efficacy Analysis

Descriptive statistics for the other efficacy endpoints will be presented by treatment group and by study visit/week where appropriate. Data from all study visits, scheduled and unscheduled, will be listed.

7.6.5.1 Change from Baseline to Week 6 in the NPSI

The NPSI, a 12-item questionnaire, assesses the different components of neuropathic pain syndromes (ie, spontaneous ongoing and paroxysmal pain, evoked pain, paresthesia/dysesthesia). 10-items related to different pain descriptors (eg, burning, squeezing, electric-shock, stabbing, tingling) allows assessment of the different dimensions of neuropathic pain and 2 items on frequency and duration of pain.

The total intensity score and the 5 subscores (burning spontaneous pain, pressing spontaneous pain, paroxysmal pain, evoked pain, and paresthesia/dysesthesia) will be calculated as:

- Total intensity score: Q1+Q2+Q3+Q5+Q6+Q8+Q9+Q10+Q11+Q12
- (Superficial spontaneous) Burning pain: Q1
- (Deep spontaneous) Pressing pain: (Q2+Q3)/2
- Paroxysmal pain: (Q5+Q6)/2
- Evoked pain: (Q8+Q9+Q10)/3
- Paresthesia/dysesthesia: (Q11+Q12)/2

Baseline will be the data collected on Day 1 at Visit 3. The change from Baseline to Week 6 in total intensity score and the 5 subscores will be summarized using standard descriptive statistics and the treatment effect will be evaluated using an ANCOVA model fitted for the fixed effects of treatment, the randomization stratum of Baseline pain severity (moderate, severe), and the continuous fixed covariate of Baseline score. The ANCOVA analysis will be performed at Week 6 only.

The adjusted mean change from Baseline to Week 6 for each treatment group and the 95% CIs will be estimated in the framework of this model, as well as the between-group differences (comparing each LX9211 treatment group to placebo) and the 95% CIs for the difference.

Summarization of the inferential statistics will include the LS means, SE of the estimates, p-values, and 2-sided 95% CIs. These statistics will be provided for the

within treatment group changes from Baseline and for the comparison of LX9211 versus placebo for the change from Baseline scores. Tabulation of the inferential results (CIs and p-values) will include the observed model findings.

7.6.5.2 Change in Question 5 of the BPI-DPN from Baseline to each post-Baseline visit

Baseline will be the data collected on Day 1 at Visit 3. For this endpoint, we will use the Question 5 of the BPI-DPN, collected at clinic visits and visit windows defined in section 6.1.2. The values collected for each post-Baseline visit and the change from Baseline at post-Baseline visits will be summarized by visit and treatment group using standard descriptive statistics. The treatment effect will be evaluated using a similar MMRM method as specified for the primary efficacy analysis of change from Baseline to Week 6.

The change from Baseline values at post-Baseline visits will be calculated as the absolute difference between Baseline value and post-Baseline values, ie,

Change from Baseline = post-Baseline value – Baseline value

7.6.5.3 Proportion of patients with ≥30% reduction from Baseline in ADPS, based on Question 5 of the BPI-DPN by week

Baseline and weekly ADPS scores will be based on the mean values as described in the primary efficacy analysis. Missing ADPS scores derivations at any week will be imputed as non-response. The frequency and percentages of patients with ≥30% reduction in pain intensity from Baseline, based on Question 5 of DPI-BPN collected each evening on the e-diary, will be presented by Week and treatment group.

7.6.5.4 Proportion of patients with ≥50% reduction from Baseline in ADPS, based on Question 5 of the BPI-DPN by week

Baseline and weekly ADPS scores will be based on the mean values as described in the primary efficacy analysis. Missing ADPS scores derivations at any week will be imputed as non-response. The frequency and percentages of patients with ≥50% reduction in pain intensity from Baseline, based on Question 5 of BPI-DPN collected each evening on the e-diary, will be presented by Week and treatment group.

7.6.5.5 Cumulative distribution function of percent change in ADPS based on Question 5 of the BPI-DPN from Baseline to Week 6 comparing the LX9211 treatment group to placebo

Baseline and Week 6 ADPS scores will be based on the same mean values as derived for the primary endpoint. A descriptive plot of the cumulative distribution function of percent change from Baseline to Week 6 in ADPS based on Question 5 of

the BPI-DPN collected each evening on the e-diary will be presented by treatment group.

% change from Baseline to Week 6 = 100*(Week 6 value – Baseline value)/ Baseline value.

7.6.5.6 Cumulative distribution function of percent change in ADPS based on Question 5 of the BPI-DPN from Week 6 to Week 11 comparing the LX9211 treatment group to placebo

Week 6 and Week 11 ADPS scores will be based on the mean weekly values as described in the primary efficacy analysis. A descriptive plot of the cumulative distribution function of percent change from Week 6 to Week 11 in ADPS based on Question 5 of the BPI-DPN collected each evening on the e-diary will be presented by treatment group. Where percent change from Week 6 to Week 11 will be defined as:

% change from Week 6 to Week 11 = 100*(Week 11 value – Week 6 value)/Week 6 value.

7.6.5.7 Change in Question 8 of the BPI-DPN from Baseline to each post-Baseline visit

Baseline will be the data collected on Day 1 at Visit 3. For this endpoint, we will use the Question 8 of the BPI-DPN, collected at clinic visits and visit windows defined in section 6.1.2. The values collected for each post-Baseline visit and the change from Baseline at post-Baseline visits will be summarized by visit and treatment group using standard descriptive statistics. The treatment effect will be evaluated using a similar MMRM method as specified for the primary efficacy analysis of change from Baseline to Week 6.

The change from Baseline values at post-Baseline visits will be calculated as the absolute difference between Baseline value and post-Baseline values, ie,

Change from Baseline = post-Baseline value – Baseline value

7.6.6 PK Analysis

C_{trough} values will be summarized at Weeks 2, 4, 6, and 11 using descriptive statistics by treatment group.

For the PK substudy, if quantifiable plasma concentrations are available, PK parameters will be derived using non-compartmental techniques, and their summarization will be based on descriptive and graphical methods and summarized for each dose level.

Plasma concentrations and time deviation data will be presented in the data listings by treatment, patient, and nominal time point. Plasma concentration data will be summarized descriptively by dose and nominal time point. Individual and mean plasma concentration versus nominal time profiles will be displayed graphically. All PK data will be presented in the data listings.

After the first 10 PK substudy patients complete the study, a blinded PK analysis may be done to confirm exposure following oral tablet administration.

As part of the PK substudy, additional samples will be collected for possible biomarker analyses. The actual and change from Baseline in biomarker/target engagement and chemokine/cytokine levels will be summarized descriptively at Weeks 2, 4, 6, and 11, by treatment group. Analyses will be performed on the mITT population with a Baseline and at least 1 valid post-Baseline data point.

7.7 Safety

7.7.1 Extent of Exposure

Duration of exposure to study drug in the double-blind Treatment Period will be defined as the total number of days of administration of the study drug:

(Date of last dose of double-blind study drug taken – date of first dose of double-blind study drug taken) + 1

Duration of exposure to study drug (days) in the double-blind Treatment Period will be summarized using descriptive statistics for each treatment group and overall for the Safety population.

The number and percentage of patients randomized and exposed to the study drug will also be presented by double-blinded treatment duration categories for each treatment group and overall for the Safety population.

- <7 days
- ≥7 and <14 days
- ≥14 and <21 days
- ≥21 and <28 days
- ≥28 and <35 days
- ≥35 and <42 days
- ≥42 days

7.7.2 Adverse Events

All AEs recorded on the eCRF will be coded using the MedDRA dictionary (Version 23 [or a later version if updated during the study]) and classified as TEAEs as follows:

- TEAEs are events with start date and time on or after the date and time of first dose of study drug during the double-blind Treatment Period or single-blinded Safety Follow-up Period, or events with start date and time prior to the date and time of first dose of study drug during the double-blind Treatment Period whose severity worsens on or after the date and time of first dose of study drug during the double-blind Treatment Period or single-blind Safety Follow-up Period.

All AE data will be listed by treatment group with TEAE status flagged in the listing. In addition, listings of treatment-emergent SAEs, TEAEs leading to discontinuation of study drug during the double-blind Treatment Period and TEAEs resulting in death will be produced.

Summary tables of TEAEs by treatment group and overall will be produced for the double-blind Treatment Period and the single-blind Safety Follow-up Period for the Safety population.

The relationship between an AE and study drug is assessed as definite, probable, possible, unlikely, or not related. A drug-related AE is an AE considered by the investigator as definitely, possibly, or probably related to study drug or with unknown/missing relationship to study drug.

An overview table will summarize the number and percentage of patients with at least 1 of the following TEAEs, where patients with more than 1 TEAE in a particular category are counted only once in that category:

- Any TEAE
- Drug-related TEAE
- Severe drug-related TEAE
- Treatment-emergent SAEs
- Drug-related treatment-emergent SAEs
- TEAE leading to study drug discontinuation
- Drug-related TEAE leading to study drug discontinuation
- TEAE leading to death

The number and percentage of patients reporting each AE will be summarized by SOC and PT for the Safety population. Tables will be sorted alphabetically by SOC.

Preferred terms will be sorted by descending overall total. The following summaries will be produced:

- TEAEs by SOC and PT
- TEAEs by PT
- TEAEs reported by at least 5% of patients in any treatment group, by SOC and PT
- TEAEs related to study drug, by SOC and PT
- TEAEs related to study drug, by PT
- TEAEs by relationship (related, or unrelated) to study drug, by SOC and PT
- TEAEs by severity, by SOC and PT
- TEAEs related to study drug by severity, by SOC and PT
- TEAEs causing discontinuation from study drug, by SOC and PT
- TEAEs related to study drug causing discontinuation from study drug, by SOC and PT
- Treatment-emergent SAEs, by SOC and PT
- Treatment-emergent SAEs related to study drug, by SOC and PT
- TEAEs leading to death, by SOC and PT
- SAEs during Screening or Run-in Periods leading to death, by SOC and PT
- The five Specific TEAEs and time to onset, by PT
- The five Specific TEAEs and AE duration, by PT
- The five Specific TEAEs and DPNP drug use, by PT
- The five Specific TEAEs and age category, by PT
- The five Specific TEAEs and sex, by PT
- The five Specific TEAEs and race, by PT
- The five Specific TEAEs and country, by PT

In the above summaries, patients with more than 1 AE within a particular SOC are counted only once for that SOC. Similarly, patients with more than 1 AE within a particular PT are counted only once for that PT. For summaries by severity, patients with multiple AEs within a particular SOC or PT will be counted under the category of their most severe AE within that SOC or PT. In a similar manner, summaries prepared by drug relationship will select the event with the greatest degree of relationship when a patient reports multiple occurrences of the same event.

The 5 specific TEAEs are defined in Section 7.6.4. For the summary of the 5 specific AEs by subgroup in the last 7 bullets, the denominator for percentage is the number of patients with the respective specific TEAEs in the double-blind treatment period for each treatment group.

The number and percentage of patients with drug interruption due to AE in the double-blind treatment period will be summarized by treatment group for the Safety population.

No statistical comparisons of AEs between treatment groups will be performed.

7.7.3 Laboratory Evaluations

Data for the following hematology, serum chemistry, lipid panel, and urinalysis analytes received from central laboratory will be listed and summarized by treatment group and visit. If data for any additional analytes are also received, then these will be listed only.

Hematology	**Serum Chemistry**	**Urinalysis**
Complete blood count (CBC) with differential Platelet count	Albumin Alkaline phosphatase Alanine transaminase (ALT) Amylase Aspartate transaminase (AST) Total bilirubin Glucose Blood urea nitrogen (BUN) Calcium Carbon dioxide Chloride Creatinine Magnesium Phosphorus Potassium Sodium Total protein Uric acid	Appearance Color Glucose Ketones Nitrite pH Protein Specific gravity Occult blood Leukocyte esterase Bilirubin Urobilinogen Urine microscopy White Blood Cell Red blood Cell Epithelial cells Bacteria Casts Crystals
Lipid panel	**Other Samples**	
High-density lipoprotein (HDL) Low-density lipoprotein (LDL) Total cholesterol Triglycerides Creatinine phosphokinase (CPK)	Pregnancy tests (females only) Urine screen (drugs of abuse and THC)	

All laboratory data will be reported in International System of Units and conventional units. Out-of-reference-range values will be flagged as high (H) or low (L) in the listings.

For analysis purposes, values preceded by a "<" or a ">" sign (ie, those below or above the limits of quantification) will be considered equal to the lower or upper limit of quantification, respectively.

Laboratory data will be summarized by visit using standard descriptive statistics by treatment group and overall for the Safety population. Changes from Baseline will also be summarized.

For hematology and serum chemistry, shift tables presenting movement in and out of reference range from Baseline to each scheduled post-Baseline visit will be provided by treatment group and overall for the Safety population. Percentages will be based on the number of patients with both non-missing Baseline and relevant post-Baseline results.

For each laboratory analyte, the Baseline value will be defined as last scheduled or unscheduled value collected prior to the first dose of study drug during the double-blind Treatment Period. Assessments carried out on the day of first study drug administration are considered to have taken place before the study drug administration, if the corresponding times have not been recorded.

7.7.4 Vital Signs

The following vital signs and weight (kg) will be listed and summarized by treatment group and visit.

- Systolic and diastolic BP (mm Hg)
- Pulse rate (beats/min [BPM])
- Respiration rate (breaths/min)
- Body temperature (°C)

Vital signs and weight data and changes from Baseline in vital signs and weight will be summarized by visit using standard descriptive statistics by treatment group and overall for the Safety population. The Baseline value will be defined as last scheduled or unscheduled value collected prior to the first dose of study drug during the double-blind Treatment Period. Assessments carried out on the day of first study drug administration are considered to have taken place before the study drug administration, if the corresponding times have not been recorded.

In addition, for vital signs, shift from Baseline (normal vs. abnormal, not clinically significant vs. abnormal, clinically significant) at each post-Baseline visit will be provided by treatment group and overall for the Safety population.

7.7.5Electrocardiograms

The following quantitative ECG measurements will be taken during the study:

- Heart rate (beats/min)
- PR interval (msec)
- QRS duration (msec)
- QT interval (msec)
- QTc interval (msec)
- Fridericia corrected QT (QTcF) interval (msec)
- RR interval (msec)

The ECG measurements and changes from Baseline in ECG will be listed and summarized by visit using standard descriptive statistics by treatment group and overall for the Safety population.

The Baseline value will be defined as last scheduled or unscheduled value collected prior to the first dose of study drug during the double-blind Treatment Period. Assessments carried out on the day of first study drug administration are considered to have taken place before the study drug administration, if the corresponding times have not been recorded.

An overall Investigator assessment of ECG will be provided (categories "normal", "abnormal, not clinically significant", "abnormal, clinically significant", "indeterminate", "not evaluable", and "unknown").

The Investigator assessment will be listed and the number and percentage of patients within each assessment category will be tabulated by visit, treatment group and overall for the Safety population. Shifts from Baseline (normal vs. abnormal, not clinically significant vs. abnormal, clinically significant) at each post-Baseline visit will be presented by treatment group and overall for the Safety population.

7.7.6 Physical Examination

Physical examination results (normal/abnormal) and details of abnormalities will be listed for each patient.

7.8 Interim Analysis

Enrollment will not be temporarily halted while data for the interim analysis is being reviewed.

An interim analysis of the primary endpoint will be performed to test for futility when approximately 50% of the planned information has been achieved. This will occur when the first 141 patients have been accrued and followed to endpoint at Week 6 or dropped out from the trial earlier, whichever event occurs first. Should a patient drop out early in the study, but return for the Week 6 visit, the Week 6 data will be used in the analysis.

To maintain continuous blinding and study integrity, analysis will be conducted by a separate unblinded team. Details of the unblinding process for the interim analysis and the resulting controlled dissemination of interim analysis data will be detailed in the Data Monitoring Committee (DMC) Charter document.

A non-binding futility boundary will be used to test treatment group differences in the primary endpoint at 50% of the original planned information. The set of boundary values will be derived by using a beta spending function and specification of a power family with value = 3.672. The monitoring boundary is constructed by assuming a 1-sided test with a per comparison Type I error rate = 0.0141, assuring an overall α= 0.025 (or a two-sided α = 0.05) for the two LX9211 versus placebo comparisons. Use of this beta spending function for futility testing is conservative and results in cumulative beta error rates of 0.015 and 0.197 at the interim and final analyses, respectively. Application of the futility analysis is to serve as a guideline and is not the only source of information used to evaluate the trial for a negative finding. Assessment of other data available at the interim analysis will be used to qualify the trial for a recommendation of futility (eg, secondary and other efficacy variables, safety data).

In addition to the above planned interim analysis, meetings for an independent DMC data reviews will be scheduled to ensure proper safety assessment during enrollment and study conduct. Initially, proposed timelines for meeting frequency to review unblinded safety data will be based on fractions of patient accrual (eg, 25% and 75% of the sample size). A final DMC meeting is planned when the study completes. The DMC will develop a charter and establish criteria when meetings are to occur, plus identify a time for the planned interim analysis should this latter event fall outside the times of the reoccurring meetings. The DMC review meetings will occur until database lock or at an earlier time deemed suitable by the DMC. This meeting schedule may be modified based on the observed patient accrual rates or signals seen in the safety data. DMC members will also receive unblinded

summaries of serious adverse events on a monthly basis to review potential emerging safety trends.

8. Changes in Planned Analysis

For NPSI, an ANCOVA model will be used to evaluate the treatment effect instead of a MMRM since the statistical analysis is conducted for the change scores at Week 6 only.

9. Data Issues

Not applicable.

10. References

Cleeland CS The Brief Pain Inventory User Guide 1991

Westfall PH, Tobias RD, Rom D, Wolfinger RD, Hochberg Y. Multiple Comparisons and Multiple Tests Using the SAS® System, Cary, NC SAS Institute Inc., 1999: 141-142.

11. Appendices

Appendix 1: Document History

Document Version, Status, Date	Summary/Reason for Changes
Version 1, Final, 23 FEB 2021	Not applicable; the first version
Version 2, Final, 23 SEP 2021	Update according to protocol amendment 4
Version 3, Final, 07 JUN 2022	Update according to dry run comments

Appendix 2: Schedule of Events

Week/Visit	Screening Period (up to 2 Weeks)	Single-blind Placebo Run-in Period	Double-blind Treatment Period				Single-Blind Safety Follow-up
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Window (days)	Week -4	Week -2	Day 1 (Baseline) [a]	Week 2	Week 4	Week 6 Or EOT / EW	Week 11[b] Or 35 Days after EOT / EW
			+3	±3	±3	±3	+7
Initiation Activities							
Informed consent	X						
Confirmation of eligibility	X	X	X				
Medical history and demographics	X						
Register patient for Screening in IXRS	X						
Register patient for single-blind Run-in period in IXRS		X					
Register patient for Randomization in IXRS			X				
Procedures/Events							
Complete physical exam [c]	X						
Symptom-related brief physical examination [c]			X	X	X	X	X
Weight	X	X	X	X	X	X	X
Height	X						
BMI calculation	X						
Patient completes HADS	X						
MNSI (Part B)	X						
Seated vital signs	X		X	X	X	X	X
Orthostatic vitals [d]			X				
12-lead ECG [e]	X		X			X	X
Assess dose compliance			X	X	X	X	X

Week/Visit Window (days)	Screening Period (up to 2 Weeks)	Single-blind Placebo Run-in Period	Double-blind Treatment Period				Single-Blind Safety Follow-up Period
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	Week -4	Week -2	Day 1 (Baseline) [a]	Week 2	Week 4	Week 6 Or EOT / EW	Week 11[b] Or 35 Days after EOT / EW
			+3	±3	±3	±3	+7
Record concomitant medications [f]	X	X	X	X	X	X	
Record SAEs [g]	X	X	X	X	X	X	X
Record AEs [h]			X	X	X	X	X
Dispense single-blind placebo		X				X	
Dispense double-blind study drug			X	X	X		
Patient Reported Outcome							
Dispense patient daily e-diary		X					
Patient completes Questions 5 and 9F of BPI-DPN on e-diary each day and records rescue medication		← Ongoing →					
Review patient daily e-diary			X	X	X	X	X
Patient completes the full BPI-DPN			X	X	X	X	X
Patient completes PGIC						X	X
Patient completes NPSI			X			X	X
Laboratory Assessments							
A1C	X						
Serum chemistry	X		X	X	X	X	X
Hematology	X		X			X	
Urinalysis with microscopy	X		X	X	X	X	X
Pregnancy test (serum) [i]	X						
Pregnancy test (urine) [i]			X			X	
FSH (females only) [j]	X						
Urine drug test for drugs of abuse and cannabinoids	X		X				
C_{trough} blood samples [k]			X	X	X	X	X

Exit Interview Substudy Assessments							
Exit interview [l]						X	

Abbreviations: A1C = hemoglobin A1C; AE = adverse event; BMI = body mass index; ECG = electrocardiogram; EOT = end of treatment; EW = early withdrawal; FSH = follicle-stimulating hormone; GFR = glomerular filtration rate; PK = pharmacokinetics; SAE = serious adverse event; IXRS = Interactive Voice/Web Response System; HADS = hospital anxiety and depression scale; BPI-DPN = brief pain inventory short form for diabetic peripheral neuropathy; PGIC = patient global impression of change

a. Day 1 window is +3 days; All laboratory assessments occur prior to first dose of double-blind study drug.
b. All patients will have a Safety Follow-up Visit 35 days/5 weeks after the last dose of study drug for collection of a plasma sample for LX9211 analysis, complete patient reported outcome assessments, and to record information on any serious adverse events (SAEs), any adverse event (AE) that was ongoing at the time of the Week 6 / EOT / EW visit, or any new events that have occurred.
c. A complete physical examination will include, at minimum, a review of the patient's general appearance, head, eyes, ears, nose and throat, neck, heart, lungs, abdomen, back and extremities, skin, and general neurological system. A symptom related brief physical exam will only occur if the patient is experiencing symptoms or AEs. If a symptom related brief physical exam is required, it should include a review of all body systems that relate to the symptoms and/or AE the patient is experiencing.
d. Orthostatic vitals will be collected on the Day 1 Visit 2 hours (±10 min.) post dose of double-blind study drug.
e. The 12- lead ECG recordings should be obtained prior to the morning study drug administration. ECG recording should be recorded either prior to phlebotomy or at least 30 minutes after phlebotomy.
f. Concomitant medications taken from 2 weeks prior to the Screening Visit through the Week 11/EOT/EW visit will be recorded.
g. All SAEs will be collected starting with signing informed consent and continue through the Week 11 Safety Follow-up Visit.
h. The collection of AEs will start after the first dose of double-blind study drug and collection will continue through the Week 11 Safety Follow-up Visit.
i. Serum pregnancy test must be performed at Screening for all females. All other required pregnancy tests can be performed via a urine test. Baseline urine test result must be reviewed prior to Randomization. The Investigator may perform additional tests at their discretion or as required by local regulations.
j. If necessary, follicle-stimulating hormone will be measured at Screening to confirm postmenopausal status.
k. C_{trough} blood samples will be drawn predose on Day 1 and at Weeks 2, 4, and 6, just prior to the dosing of study drug on the day of the clinic visit. At the Week 11/EOT/EW Safety Follow-up Visit, a final sample will be collected.
l. Qualitative patient interviews are to be completed by an independent third-party vendor within 2 weeks following the Week 6 Visit or Early Withdrawal Visit.

Appendix 3: Brief Pain Inventory – DPN (BPI-DPN)

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Brief Pain Inventory (Short Form) - DPN

Date:____/____/____ Time:_____

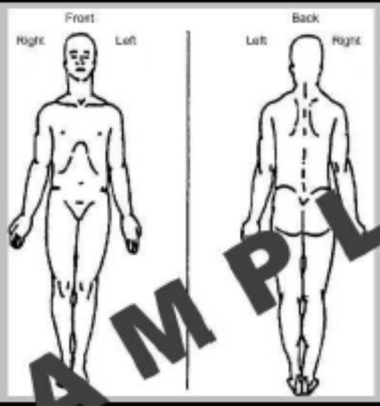
Name:_____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain due to your diabetes by circling the one number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

4. Please rate your pain due to your diabetes by circling the one number that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

5. Please rate your pain due to your diabetes by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

6. Please rate your pain due to your diabetes by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

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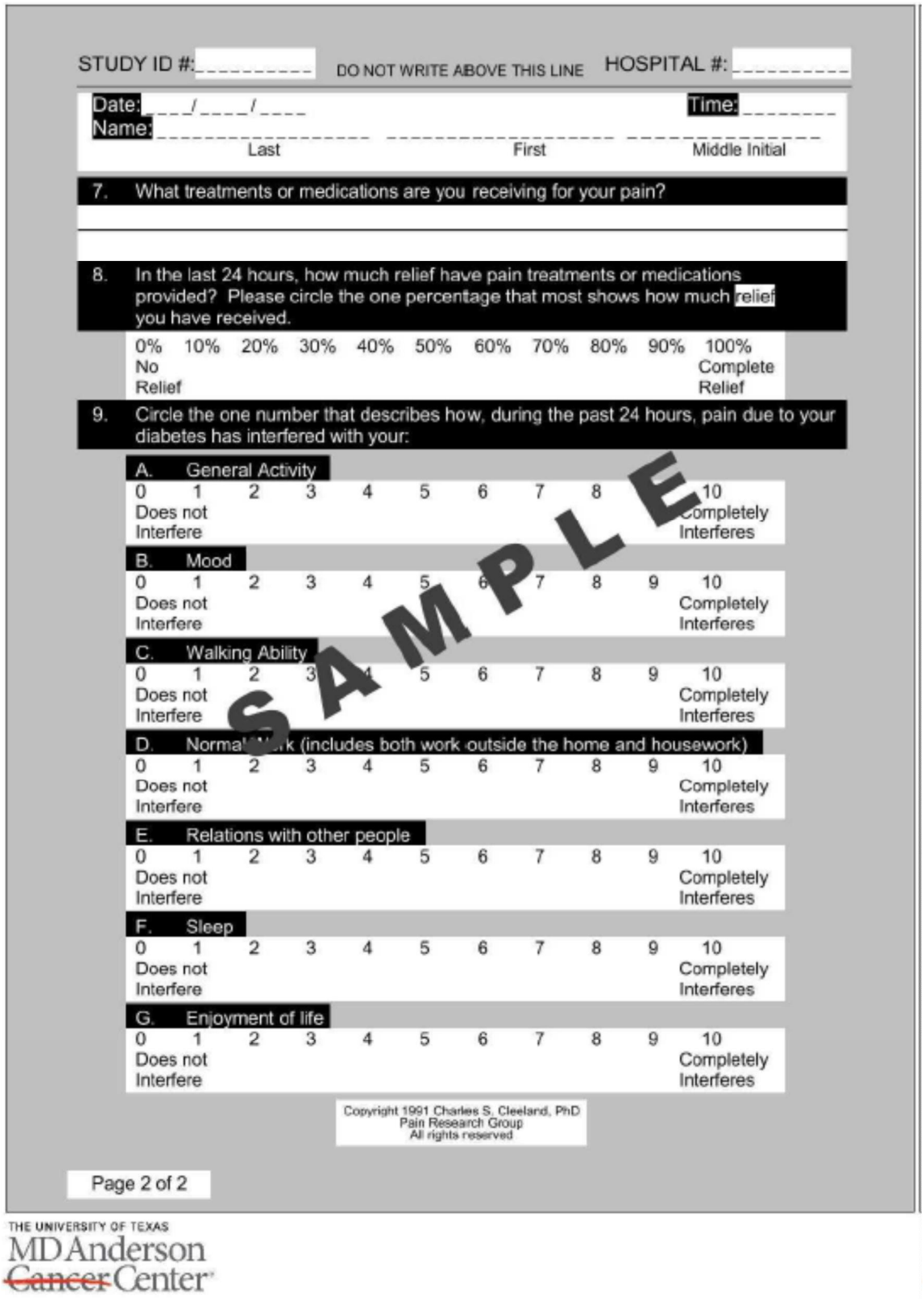

STUDY ID #:_____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #:_____

Date:____/____/____ Time:_____
Name:_____ _____ _____
Last First Middle Initial

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0% No Relief 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain due to your diabetes has interfered with your:

A. General Activity
0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

B. Mood
0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

C. Walking Ability
0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

D. Normal Work (includes both work outside the home and housework)
0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

E. Relations with other people
0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

F. Sleep
0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

G. Enjoyment of life
0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

SAMPLE

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Appendix 4: Patient Global Impression of Change (PGIC)

PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC)

Since the start of the study, my overall status is:

✓*one box only:*

[1] ☐ Very Much Improved
[2] ☐ Much Improved
[3] ☐ Minimally Improved
[4] ☐ No Change
[5] ☐ Minimally Worse
[6] ☐ Much Worse
[7] ☐ Very Much Worse

(US/English)

USA/English – Version of 05 April 2005
PGI-G_T01.0_ID2000-2007_eng-USori.doc

Appendix 5: Neuropathic Pain Symptom Inventory (NPSI)

NEUROPATHIC PAIN SYMPTOM INVENTORY (NPSI)

Correspondence: Dr Didier Bouhassira
INSERM U-792, Centre d'Evaluation et de Traitement de la Douleur
Hôpital Ambroise Paré, 92100 Boulogne-Billancourt, France
didier.bouhassira@apr.ap-hop-paris.fr

Date: .....

First Name: ..... **Last Name:** .....

Sex: .....

Age: .....

You are suffering from pain due to injury or disease of the nervous system. There may be several types of this pain. You may have spontaneous pain, that is pain in the absence of any stimulation, which may be long-lasting or occur as brief attacks. You may also have pain provoked or increased by brushing, pressure, contact with something cold on the painful area. You may feel one or several types of pain. This questionnaire has been developed to help your doctor to better evaluate and treat the various types of pain you feel.

1

*We wish to know if you feel spontaneous pain, that is pain without any stimulation. For each of the following questions, please circle the number that best describes the **average severity of your spontaneous pain during the past 24 hours**. Circle the number 0 if you have not felt such pain. (Circle one number only.)*

Q1/. Does your pain feel like burning?

No burning	0	1	2	3	4	5	6	7	8	9	10	Worst burning imaginable

Q2/. Does your pain feel like squeezing?

No squeezing	0	1	2	3	4	5	6	7	8	9	10	Worst squeezing imaginable

Q3/. Does your pain feel like pressure?

No pressure	0	1	2	3	4	5	6	7	8	9	10	Worst pressure imaginable

Q4/. **During the past 24 hours**, your spontaneous pain has been present:

Tick the response that best describes your case.

Permanently	/_/
Between 8 and 12 hours	/_/
Between 4 and 7 hours	/_/
Between 1 and 3 hours	/_/
Less than 1 hour	/_/

*We wish to know if you have brief attacks of pain. For each of the following questions, please circle the number that best describes the **average severity of your painful attacks during the past 24 hours**. Circle the number 0 if you have not felt such pain. (Circle one number only.)*

Q5/. Does your pain feel like electric shocks?

No electric shocks	0	1	2	3	4	5	6	7	8	9	10	Worst electric shocks imaginable

Q6/. Does your pain feel like stabbing?

No stabbing	0	1	2	3	4	5	6	7	8	9	10	Worst stabbing imaginable

Q7/. **During the past 24 hours**, how many of these pain attacks have you had?

Tick the response that best describes your case.

More than 20	/_/
Between 11 and 20	/_/
Between 6 and 10	/_/
Between 1 and 5	/_/
No pain attack	/_/

*We wish to know if you feel pain provoked or increased by brushing, pressure, contact with something cold on the painful area. For each of the following questions, please circle the number that best describes the **average severity of your provoked pain during the past 24 hours**. Circle the number 0 if you have not felt such pain. (Circle one number only.)*

Q8/. Is your pain provoked or increased by brushing on the painful area?

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst pain imaginable

Q9/. Is your pain provoked or increased by pressure on the painful area?

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst pain imaginable

Q10/. Is your pain provoked or increased by **contact** with something cold on the painful area?

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst pain imaginable

*We wish to know if you feel abnormal sensations **in the painful area**. For each of the following questions, please circle the number that best describes the **average severity of your abnormal sensations during the past 24 hours**. Circle the number 0 if you have not felt such sensations. (Circle one number only.)*

Q11/. Do you feel pins and needles?

No pins & needles	0	1	2	3	4	5	6	7	8	9	10	Worst pins & needles imaginable

Q12/. Do you feel tingling?

No tingling	0	1	2	3	4	5	6	7	8	9	10	Worst tingling imaginable

RESULTS

TOTAL SCORE	SUBSCORES
1 – Q1 = ...	(SUPERFICIAL SPONTANEOUS) BURNING PAIN: Q1= ...../10
2 – (Q2+Q3) = ...	(DEEP SPONTANEOUS) PRESSING PAIN: (Q2+Q3)/2 = .../10
3 – (Q5+Q6) = ...	PAROXYSMAL PAIN: (Q5+Q6)/2 = .../10
4 – (Q8+Q9+Q10) = ...	EVOKED PAIN: (Q8+Q9+Q10)/3= ...../10
5 – (Q11+Q12) = ...	PARESTHESIA/DYSESTHESIA: (Q11+Q12)/2 = .../10
(1+2+3+4+5) = .../100	

3

Appendix 6: Hospital Anxiety and Depression Scale (HADS)

FOLD HERE

Hospital Anxiety and Depression Scale (HADS)

GL Assessment

Name: _____ Date: _____

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

FOLD HERE

A

I feel tense or "wound up"
3 Most of the time
2 A lot of the time
1 From time to time, occasionally
0 Never

I enjoy the things I used to enjoy
Definitely
Not quite so much
Only a little
Hardly at all

I get a sort of frightened feeling as if something awful is about to happen
3 Very definitely and fairly badly
2 Yes, but not too badly
1 Sometimes, but it doesn't worry me
0 Never

I can laugh and see the funny side of things
As much as I always could
Not quite so much now
Definitely not so much now
Never

Worrying thoughts go through my mind
3 A great deal of the time
2 A lot of the time
1 Not too often
0 Almost never

I feel cheerful
Never
Not often
Sometimes
Most of the time

I can sit at ease and feel relaxed
0 Always
1 Usually
2 Not often
3 Never

I feel as if I am slowed down
Nearly all the time 3
Very often 2
Sometimes 1
Never 0

A D

HADS - United States/English - Version of 30 Jan 17 - Mapi.
ID058041 / HADS_AUS.0_eng-US.doc

I get a sort of anxious feeling like "butterflies" in the stomach		
Never	0	
Occasionally	1	
Often	2	
Very often	3	
I have lost interest in my appearance		
Definitely		3
Often I don't take as much care as I should		2
Sometimes I don't take as much care as I should		1
I take just as much care as ever		0
I feel restless as if I have to be on the move		
Definitely	3	
Quite a lot	2	
Not very much	1	
Never	0	
I look forward with enjoyment to things		
As much as I ever have		0
Somewhat less than I used to		1
Much less than I used to		2
Rarely		3
I get sudden feelings of panic		
Very often	3	
Often	2	
Not very often	1	
Never	0	
I can enjoy a good book, radio or television program		
Often		0
Sometimes		1
Not often		2
Very seldom		3

Please make sure you have answered all the questions.

	A	D
TOTAL		

HADS - United States/English - Version of 30 Jan 17 - Mapi.
ID058041 / HADS_AU5.0_eng-US.doc

Type of Approval (select one) : ☒ **SAP** ☐ **Initiation of Programming**

Sponsor Name:	Lexicon Pharmaceuticals, Inc		
Sponsor Protocol/CIP ID:	LX9211.1.201-DPN	**Labcorp Study ID:**	000000198624
SAP text filename:	LX9211.1.201-DPN SAP Final v3.0 _07JUN2022	**TFL shells filename:**	LX9211.1.202-DPN TFL Shells Final v1.0_07JUN2022
Version:	3	**Date:**	08JUN2022

Labcorp Approval:

Lead Statistician

Approval Signature Print Name Job Title Date	[redacted] [redacted] Principal Statistician I approved this document [redacted]

Sponsor Approval:

By signing below when the statistical analysis plan (SAP) is considered final, the signatories agree to the analyses to be performed for this study and to the format of the associated tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the Analysis Dataset Model (ADaM) datasets and TFLs based on these documents can proceed. Any modifications to the SAP text and TFL shells made after signing may result in a work-scope change.

Approval Signature Print Name Job Title Date	[redacted] Digitally signed by [redacted] DN: cn=[redacted], o=Lexicon Pharmaceuticals, ou=[redacted], Biostatistics, email=[redacted] c=US Date: [redacted]

Please scan/email completed form to the Lead Statistician listed below:

Printed Name/Title:	[redacted] /Principal Statistician
Email:	[redacted]

Interviews to Assess the Patient Experience With LX9211 for the Treatment of Diabetic Peripheral Neuropathic Pain

Final Qualitative Analysis Plan

April 2, 2020

Prepared for

[redacted]
Lexicon Pharmaceuticals, Inc.
E-mail: [redacted]

[redacted] **PhD**
Lexicon Pharmaceuticals, Inc.
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RTI-HS Project No. 0305678

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RTI Health Solutions (RTI-HS) is pleased to deliver this qualitative analysis plan for the interviews planned with patients enrolled in the LX9211-102 DPN[1] (RELIEF-DPN 1) clinical trial in the United States. The purpose of this document is to provide a detailed and comprehensive description of the qualitative and, when applicable, quantitative analytic methods that will be used to summarize the patient interview data.

1 STUDY BACKGROUND AND DESIGN

Lexicon Pharmaceuticals, Inc. (Lexicon) is conducting a phase 2 clinical trial[1] to evaluate the efficacy of LX9211, an oral product for the treatment of diabetic peripheral neuropathic pain (DPNP). As part of the clinical trial, RTI-HS, in collaboration with Lexicon, plans to conduct qualitative interviews with a subset of patients from the study that will supplement the patient-reported data gathered in the clinical trial and help to further understand and describe patients' experiences with DPNP and LX9211.

Data collected during in-depth qualitative interviews will provide a deeper understanding of patients' perceptions of and experiences with DPNP and LX9211 and the relevance and clinical meaningfulness of symptom improvements (e.g., reduction in pain) to patients. The semistructured telephone interviews will be conducted with a subset of English-speaking clinical trial participants (up to 60 patients) who complete or terminate early from the 6-week double-blind treatment phase of the trial.

The overall objective of the qualitative interviews is to gain a more comprehensive understanding of patient experiences with DPNP and LX9211 treatment by collecting information that may not be captured adequately via traditional clinical outcomes assessments. Specifically, the objectives of the qualitative interviews are to obtain a better understanding of the perspectives of patients with DPNP on the following:

- Disease-related burden
- Impact of the disease on patients' lives before starting the clinical trial
- Satisfaction with DPNP treatments used prior to the clinical trial
- Most important to treat and most bothersome aspects of DPNP
- Expectations of study drug
- General experiences with study drug
- Benefits and impact of those benefits
- Importance of improvements experienced during the clinical trial (if experienced)
- Impact of the study drug on daily life/functioning

[1] A Phase 2, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of LX9211 in the Treatment of Diabetic Peripheral Neuropathic Pain (Protocol Number LX9211.201)

- How well the study drug addresses most important/bothersome symptoms
- Satisfaction with and reason(s) for satisfaction or dissatisfaction (if applicable) with the study drug

2 ANALYSIS OBJECTIVES

Analysis of the interview data will focus on answering the research questions (described in Sections 2.1 and 2.2), which expand on the study objectives described above and form the conceptual basis for the interview guide (Appendix A). Additionally, selected research questions will be further analyzed within the context of clinical trial treatment groups (to be provided by Lexicon). This process and the anticipated analysis by treatment group are further described in Section 4.3.

Analysis for the initial draft of the summary report will be based on blinded data. The final summary report will present the analysis of unblinded data (LX9211 treatment groups and placebo).

2.1 Background Information and Pre-Study Experiences

- Describe study participants (sex, age, age when first diagnosed with diabetes, age at onset of DPNP symptoms)
- Summarize satisfaction with DPNP treatment(s) and difficulty managing DPNP before clinical trial
- Identify DPNP symptoms[2] before the clinical trial
  - Spontaneous descriptions of pain/sensations
    - The presence of specific symptoms/sensations (i.e., numbness/dead feeling, tingling/pins and needles, weakness, very sensitive/heightened sensitivity to touch and pressure) will be probed (if not spontaneously reported by the interview participant) per the interview guide (Appendix A)
  - Location of DPNP and severity of DPNP in each location
  - Most bothersome symptom(s)/sensations
- Describe the impact of DPNP on patients before participating in the clinical trial
  - What impacts associated with DPNP (e.g., on daily activities, mobility, mood/emotions, self-care, sleep) are reported most frequently by patients?
    - The presence of specific impacts will be probed (if not spontaneously reported by interview participants) (daily activities at work and/or home, mobility, mood/emotions, self-care, sleep)

[2] List of symptoms anticipated are included in interview guide and codebook. **Note**: codes will be modified as needed based on content reported in patient interviews.

  - What about DPNP and/or its treatment is most bothersome to the interview participants (e.g., if the most bothersome issues are symptom related or treatment related)?
- Identify interview participants' expectations of treatment
  - Reasons for participating in the clinical trial
  - What symptoms do interview participants most want to see treated with the study drug?
    - Perceived importance of each symptom improvement

2.2 Experiences During Treatment

- What improvements did interview participants see in their DPNP symptoms during clinical trial?
  - The presence of specific symptoms will be probed (if not spontaneously reported by interview participants) per the interview guide (Appendix A)
- If improvements were noticed, summarize when interview participants first reported experiencing these changes and which change was noticed first (if more than one improvement)
- Summarize the improvements identified as the most important as well as importance ratings
- Summarize the impact of improvements noticed as a result of study drug
  - Specific impacts will be probed (if not spontaneously reported by the interview participant) (daily activities at work and/or home, mobility, mood/emotions, self-care, sleep)
- Summarize the drug's ability to treat those symptoms identified as the most bothersome or important to treat
- Assess interview participants' clinical trial treatment satisfaction
  - What factors or considerations influenced satisfaction ratings?
  - How many interview participants expressed a desire to continue taking the study drug and why?
  - How many interview participants expressed a preference for the study drug over previous medication(s) for DPNP and why?

3 ANALYSIS DATA SET AND SOFTWARE

Interview data analysis will be performed using anonymized interview transcripts. The majority of the planned analyses will be conducted using ATLAS.ti version 7.5 qualitative data analysis software. Other software will also be used as appropriate for the generation of

descriptive analyses, including SAS for Windows (version 9.4 or higher) and Microsoft Excel 2017.

3.1 Data Transcription

Upon interview completion, each interview will be transcribed and prepared in a standardized, quality-checked manner with each transcription undergoing multiple levels of review. First, the interviews will be transcribed by a qualified medical transcriptionist. All personally identifying data will be removed from the transcript at this stage. Next, a second medical transcriptionist will review the draft, typed transcript while listening to the recorded interview and will implement any necessary corrections or edits. A review of the transcripts by the technical team will occur during the coding process. Before delivery to the client, all transcripts will also be reviewed by RTI-HS editors to check for any spelling and/or punctuation errors prior to finalization of the transcripts for analysis.

4 ANALYTICAL METHODS

4.1 Codebook Development

Thematic analysis methods will be used to analyze the interview transcript data (Braun and Clarke, 2006). An initial coding framework (Draft 1; 25 February 2020) based on the final interview guide is presented in Appendix B. Finalization of the codebook will be an iterative process based on the interview data. Specifically, it is anticipated that new codes will be added to the codebook as new concepts (e.g., potential DPNP symptoms, impacts) are identified during transcript review.

4.2 Transcript Coding

Each interview transcript will be coded in accordance with the codebook. To ensure consistency in coding, approximately 10% (n = 6) of the transcripts will be double coded, meaning that two different people will code these transcripts. Any discrepancies found between these codes will be resolved by the two coders and in discussion with the Project Director.

4.3 Qualitative Data Analysis

Standardized qualitative research methods will be applied during the conduct of each interview (Willis, 1999; Boeije, 2002). Specifically, immediately following the receipt of each transcript, RTI-HS will begin the thematic analysis process. Using field notes and transcripts, thematic analysis methods will be used to analyze the interview transcript data. Important concepts and dominant trends will be identified in each interview. These individual interview results will then be compared across interviews to allow for the

generation of themes or patterns in interview participants' responses. As noted above, the qualitative data analyses will be facilitated through the use of ATLAS.ti and other software (e.g., Microsoft Excel).

4.4 Quantitative Data Analysis

The ATLAS codebook (Appendix B) includes codes to facilitate quantitative summarization (descriptive analysis) of interview participants' reports related to DPNP symptoms and impacts. In the analysis and reporting of frequencies or counts of these concepts, only unique mentions per code per patient will be counted.

- Frequency and percentage of interview participants reporting each DPNP symptom/sensation before the clinical trial
- Frequency and percentage of interview participants reporting pain in specific locations (e.g., hands, arms, feet)
- Frequency and percentage of interview participants reporting a specific location (e.g., hands, arms, feet) as the location where their pain is most severe
- Frequency and percentage of interview participants reporting a specific location (e.g., hands, arms, feet) as the most bothersome
- Frequency and percentage with which each symptom or sensation was reported as the most bothersome
- Frequency and percentage of DPNP impacts reported before the clinical trial
- Frequency and percentage of a DPNP symptom being reported as the most important to treat prior to starting the clinical trial

Descriptive statistics (frequencies, mean, range) will be computed for the following assessments for the overall interview sample and by treatment assignment, as provided by Lexicon (LX9211 treatment [10 mg or 20 mg] or placebo):

- Clinical and demographic characteristics reported (e.g., sex, age, age of diagnosis of diabetes, age at onset of DPNP symptoms)
- Frequency and percentage of interview participants reporting specific symptom improvements during the clinical trial
- Frequency and percentage of improvement in a symptom (reported during the clinical trial) being reported as the most important improvement
- Frequency and percentage of specific impacts of symptom improvements being reported across interview participants

- Satisfaction with treatment before and after the clinical trial
  - 0 = not at all satisfied, 1 = a little satisfied, 2 = moderately satisfied, 3 = quite satisfied, and 4 = very satisfied
- Difficulty managing DPNP before the clinical trial
  - 0 = not at all difficult, 1 = a little difficult, 2 = moderately difficult, 3 = quite difficult, 4 = very difficult
- Ratings for how important it would be for a treatment to improve specific symptoms
  - 1 = not at all important, 2 = a little important, 3 = moderately important, 4 = very important, 5 = extremely important
- Importance ratings for any symptom reported as improved during the clinical trial
  - 1 = not at all important, 2 = a little important, 3 = moderately important, 4 = very important, 5 = extremely important
- Preference of study drug or a previous medication
- Desire to continue study drug (yes/no)

As noted previously, analysis will initially be conducted on blinded data, and will be presented in aggregate in the first draft of the summary report (Section 5). After provision of the treatment assignment data (from Lexicon) RTI-HS will conduct analyses by treatment group.

For the analysis correlating/examining the relationship between selected interview (e.g., treatment satisfaction, desire to continue on treatment and treatment preference) and clinical trial results (e.g., baseline average daily pain score and the change in average daily pain score; up to 5 variables, to be decided in collaboration with Lexicon), it is anticipated that Lexicon will provide RTI-HS with clinical data in one of two formats:

- Clinical Data Interchange Standards Consortium (CDISC)-compliant data sets in SAS Analysis Data Model (ADaM) format

  OR

- A SAS data set organized as one row per patient and structured such that a variable measured at multiple time points is represented as multiple variables (columns) per patient (rather than multiple observations or rows per patient).

Lexicon will also provide RTI-HS with codebooks and any other relevant data documentation and will be available to answer questions regarding the data and appropriate analysis variables.

5 REPORTING

RTI-HS will prepare and submit to Lexicon a summary report describing the interview methods and results. The draft report will be prepared using blinded data; the final summary report will incorporate treatment assignment provided by Lexicon. Specifically, this report will include results pertaining to each of the research questions outlined in Section 2. Tables will be prepared to summarize the results of the descriptive analyses outlined in Sections 4.3 and 4.4. Table shells for use in the final report are provided in Appendix C (these same shells will be used to inform the draft report; however, data will be presented in aggregate on blinded data).

Although adverse event elicitation and description are not an objective of this study, any adverse events (as described in the study procedure guide) reported in the context of the patient interviews will be summarized in tabular format in the summary report. Sites will be notified of any reported adverse events, and all reported events will be reconciled by Lexicon or their designee with the clinical trial safety database to ensure no new signals were detected.

6 REFERENCES

Boeije HA. Purposeful approach to the constant comparative method in the analysis of qualitative interviews. Qual Quant. 2002;36:391-409.

Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol. 2006;3(2):77-101.

Willis G. Cognitive interviewing: a "how to" guide. Research Triangle Park, NC: RTI International; 1999.

Appendix A. Final Interview Guide

Phase 2 Clinical Trial of LX9211 for the Treatment of Diabetic Peripheral Neuropathic Pain

Exit Interviews

I. Introduction ~ 5 min

[Introduce interviewers; confirm participant's first name **before** starting the interview; confirm with the participant that now is still a convenient time for the interview—if the patient expresses any concerns or hesitancy (or based on the interviewer's judgment), reschedule the interview.]

[Remind participant about key elements listed in consent form]

The purpose of today's interview is to learn more about your experiences, specifically:

- Your experiences with diabetic peripheral neuropathic pain (we will refer to this as neuropathic pain) and its treatments
- Any expectations about the study drug you had before starting the clinical trial
- Your experiences with the drug you received in the clinical study and
- Any improvements you may have noticed from the study drug.

The information you provide today will be used to help the study sponsor better understand people's experiences with nerve pain associated with their diabetes and their experiences with the study drug.

We invite you to speak openly and share your opinions freely. We value everything you tell us and be assured that there are no wrong answers.

This information is in the study consent form, but as a reminder…

- Our discussion today is scheduled to take about 60 minutes.
- We are audio recording and transcribing all interviews to make sure we do not miss any important information. Also, this will help us write a summary report.
- The transcripts from the interviews will be given to the study sponsor at the end of this study, with only your study ID number attached. All names mentioned during the interview will be removed from the transcript.
- Finally, please remember that today's interview is completely voluntary; you can take a break or end the discussion at any time.

If you report a side effect during today's call that is potentially related to the study drug, I will have to notify your clinical site. They will determine whether your study doctor needs to follow-up with you for more information.

Additionally, the clinical study sponsor will share limited data from the clinical study with us so that we can better understand experiences of participants in the study. For example, they may share with us scores from some of the questionnaires you completed as part of the clinical study and your responses to certain questions about how well the drug worked for you.

Do you have any questions before we begin? [Answer any questions.]

START RECORDING

[Once the recording starts, the interviewer will verbally record the participant's clinical study ID and interview date for the audio]

We have started the audio recording. Do we have your permission to continue with the interview?

☐ Yes → **CONTINUE**

☐ No → **STOP INTERVIEW**

II. Background Information and Prestudy Experiences ~ 10 min

[RECORD]

First, I would like to learn a little more about you and about your experiences with diabetic neuropathic pain

1. **How old are you? _____ years [Confirm from recruitment grid]**
2. **About how old were you when you were diagnosed with diabetes? _____ (years old)**
3. **About how long ago did you start to experience neuropathic pain associated with your diabetes_____ (months/years)**

4. **Before starting the study, in your own words, what did this pain feel like?**

   [If not reported spontaneously probe for the presence of the following]

   a) **Numbness/dead feeling**

   b) **Tingling/pins and needles**

   c) **Weakness**

   d) **Very sensitive/heightened sensitivity to touch and pressure**

5. **Before starting the study, where did you experience your neuropathic pain?**

   a) **Hands**

   b) **Arms**

   c) **Feet**

   d) **Legs**

   e) **Other _____**

6. **[If experienced in more than 1 location] Were there specific locations where the pain was more severe than <u>others before starting the clinical trial</u>? [If yes] Which ones?**

7. **[If more than one symptom experienced] Were specific symptoms more bothersome to you than others before starting the clinical trial? [If necessary, remind patient of the symptoms reported in Q4]. [If yes] Which ones?**

8. **<u>Before starting the clinical trial</u>, overall, how satisfied were you with your neuropathic pain treatment(s)?**

   ☐ 0 = Not at all satisfied

   ☐ 1 = A little satisfied

   ☐ 2 = Moderately satisfied

   ☐ 3 = Quite satisfied

   ☐ 4 = Very satisfied

   - Tell me why you selected that answer.

9. **Before starting the clinical trial, how easy or hard was it for you to manage your neuropathic pain?**

   ☐ 0 = Not at all difficult

   ☐ 1 = A little difficult

   ☐ 2 = Moderately difficult

   ☐ 3 = Quite difficult

   ☐ 4 = Very difficult

   - Tell me why you selected that answer.

III. Prestudy Impact/Burden Of DPNP ~ 10 min

10. **Before starting the study, what impact did diabetic neuropathic pain have on your life, if at all? [Allow for spontaneous reports of impacts. Specific probes are listed below]**

11. **How, if at all, did this pain affect your life before the study? [Probe for impact areas if not spontaneously reported]…**

    a) Daily activities? What kinds of daily activities were impacted?

    - Are there things you could not do because of the pain that you wanted to do?

    b) Mobility (e.g., walking; using stairs; getting up/down from chair or toilet)

    c) Mood/emotions (e.g., depressed mood, anxiety, irritability, anger)

    d) Self-care (e.g., bathing or dressing self; using utensils)

    e) Sleep

12. **What was it about your neuropathic pain or its treatment that bothered you the most before starting the study? [Probe to understand if most bothersome issues are issues related to the pain and/or are treatment-related]**

    Why does [repeat most bothersome issue] bother you?

IV. Prestudy Treatment Expectations ~ 5 min

13. Thinking back to before you started the clinical trial, what were some of the reasons you decided to participate in the trial?

a) Were some reasons more important to you than others? [If yes] Which ones?

14. Before starting the clinical trial, were there specific symptoms/problems that you most wanted the study drug to help? Which ones? Why?

15. How important to you would it be for a neuropathic pain treatment to improve? [Use the 1-to-5 rating scale below for each symptom the patient reports – examples listed below. Repeat scale as often as needed]

- ☐ 1 = Not at all important
- ☐ 2 = A little important
- ☐ 3 = Somewhat important
- ☐ 4 = Very important
- ☐ 5 = Extremely important

a) Pain

b) Numbness

c) Tingling/pins and needles

d) Weakness

V. During Study Experiences ~ 15 min

Now I would like to talk to you about your experiences during the clinical study. So, thinking about your experiences while you were taking the study drug….

16. **What were your overall impressions of the study drug?**

17. **What improvements, if any, did you notice while taking the study drug?**
[Ask the participant to describe each improvement reported. Allow for spontaneous reports of improvements in symptoms/pain. If not already mentioned, probe to see if the symptoms experienced before the study improved, if so, have the participant describe the improvement and rate the importance of the improvement below]

18. **Please rate the importance of the improvement in [SYMPTOM from Q4] on the following scale (from 1 to 5). I will read the scale to you:**

☐ 1 = Not at all important

☐ 2 = A little important

☐ 3 = Moderately important

☐ 4 = Very important

☐ 5 = Extremely important

Why?

[If improvements noticed] How soon after receiving the study drug did you notice these improvements?

a) What, specifically, did you notice first?

VI. Impact of Improvements [If no improvements, skip to Q 23] ~ 10 min

19. Thinking about the improvements [Refer back to improvements listed above] you noticed as a result of the study drug, which are the most important to you? Why?

20. Thinking about the improvements you have seen from the study drug; how did these improvements affect you in your daily life? [Allow for spontaneous responses]

[If not reported spontaneously] How, if at all, did these improvements affect your…

a) Daily activities? What kinds of daily activities were impacted?

- Are there things you can now do or do better because of improvements in neuropathic pain?

b) Mobility (e.g., walking; using stairs; getting up/down from chair or toilet)

c) Mood/emotions (e.g., depressed mood, anxiety)

d) Self-care (e.g., bathing or dressing self; using utensils)

e) Sleep

21. You mentioned that that [insert response from Q14] bothered you the most. How, if at all, did the study drug improve these issues?

VII. Treatment Satisfaction and Preference ~ 5 min

22. Overall, how satisfied are you with the study drug as a treatment for diabetic neuropathic pain?

- ☐ 0 = Not at all satisfied
- ☐ 1 = A little satisfied
- ☐ 2 = Moderately satisfied
- ☐ 3 = Quite satisfied
- ☐ 4 = Very satisfied

a) Tell me why you selected that response. [Probe to better understand what specifically influenced participant's response to this question]

23. Thinking about the study drug compared to the neuropathic pain treatment(s) you had tried before the study, which did you prefer:

☐ Study drug

☐ A previous medication

Why?

24. Would you have continued taking the study drug if you could have?

☐ Yes

☐ No

Why?

VIII. Summing Up ~ 2 min

Thank you for sharing your thoughts and experiences with us today. This information is very valuable and will help the study sponsors understand more about patients with diabetic neuropathic pain and the impact of the study drug.

Is there anything else you think we should know (i.e., anything we should have asked but didn't)?

[Thank participant again and end call]

Appendix B. ATLAS Codebook (Draft 1; 17 February 2020)

PARTICIPANT INTERVIEWS: LX9211 DRAFT CODEBOOK: GENERAL CODING POINTS

- Operational definitions are for coder reliability, not necessarily analytic interpretation
- Codes and their operational definitions evolve based on the transcript text reviewed. These codes and their definitions are subject to change throughout the coding process.

Code		Operational Definition
1.0	**Treatment Assignment**	**Treatment assignment data provided by Lexicon**
1.1	Treatment_10mg	Patient was on study drug (10 mg)
1.2	Treatment_20mg	Patient was on study drug (20 mg)
1.3	Placebo	Patient was on placebo
2.0	**Background**	**Code response to background questions**
2.1	Age at diabetes diagnosis	Response to the question "About how old were you when you diagnosed with diabetes?"
2.3	Time since DPNP symptoms began	Response to the question "About how long ago did you start to experience neuropathic pain associated with your diabetes?"
3.0	**DPNP Symptoms Before Study**	**Code all information about the symptoms participant experienced before the clinical trial**
3.1	Symptom_Numbness	Neuropathic pain described as numbness or dead feeling
3.2	Symptom_Tingling	Neuropathic pain described as tingling or pins and needles
3.3	Symptom_Weakness	Neuropathic pain described as weakness
3.4	Symptom_Sensitivity	Neuropathic pain described as very sensitive or sensitivity to touch and pressure
3.5	Symptom_Other descriptions of pain	Any other descriptions of neuropathic pain
3.6	Location_Hands	Neuropathic pain in the hands
3.7	Location_Arms	Neuropathic pain in the arms
3.8	Location_Feet	Neuropathic pain in the feet
3.9	Location_Legs	Neuropathic pain in the legs
3.10	Location_Other	Neuropathic pain in any other location
3.11	Location_Severe	Response to the question "Were there specific locations where the pain was more severe than others before starting the clinical trial? Which ones?"
3.12	Symptom_Bothersome	Response to the question "Were specific symptoms more bothersome to you than others before the clinical trial? Which ones?"

Code		Operational Definition
4.0	**Pre-trial Satisfaction**	**Code responses to satisfaction and management questions. Code both quantitative response and reasons why.**
4.1	Pre-trial treatment satisfaction	Responses to the questions "Before starting the clinical trial, overall, how satisfied were you with your neuropathic pain treatment?" and "Tell me why you selected that answer."
4.2	Pre-trial pain management	Responses to the questions "Before starting the clinical trial, how easy or hard was it for you to manage your neuropathic pain?" and "Tell me why you selected that answer."
5.0	**DPNP Impacts Before Clinical Trial**	**Code response to the question "Before starting the study, what impact did diabetic neuropathic pain have your life, if at all" and follow-up probes.**
5.1	Impact_daily activities_work	Impact on any gainful activities (e.g., absenteeism, productivity)
5.2	Impact_daily activities_home	Impact on activities completed at home (running a household, caring for family)
5.3	Impact_mobility	Impact on walking, using stairs, getting up/down from a chair or toilet, etc.
5.4	Impact_mood/emotions	Impact on mood/emotions/feelings, such as depressed mood, anxiety, irritability, anger
5.5	Impact_self-care	Impact on ability to engage in self-care activities such as bathing, dressing, using utensils
5.6	Impact_sleep	Impact on ability to get to sleep or stay asleep
5.7	No_impact	Patient reports no impacts
5.8	Most bothersome problem – DPNP_Symptom	Response to the question "What was it about your neuropathic pain or treatment that bothered you the most before starting the study?" for all symptom responses and related probes
5.8	Most bothersome problem – DPNP_Treatment	Response to the question "What was it about your neuropathic pain or treatment that bothered you the most before starting the study?" for all treatment responses and related probes

Code		Operational Definition
6.0	**Clinical Trial Desires/Expectations**	**Code responses to questions related to prestudy treatment expectations**
6.1	Reasons_CT	Response to question "Thinking back to before you started the clinical trial, what were some of the reasons you decided to participate in the trial?" and "Were some reasons more important to you than others? Which ones?"
6.2	Sx_Treat_CT	Response to question "Before starting the clinical trial, were there specific symptoms that you most wanted the study drug to help? Which ones? Why?"
6.3	Sx_Treat_Importance_Numbness	Response to question "How important would it be to you for a neuropathic pain treatment to improve numbness?"
6.4	Sx_Treat_Importance_Tingling	Response to question "How important would it be to you for a neuropathic pain treatment to improve tingling?"
6.5	Sx_Treat_Importance_Weakness	Response to question "How important would it be to you for a neuropathic pain treatment to improve weakness?"
6.6	Sx_Treat_Importance_Sensitivity	Response to question "How important would it be to you for a neuropathic pain treatment to improve sensitivity?"
6.7	Sx_Treat_Importance_Other	Response to question "How important would it be to you for a neuropathic pain treatment to improve [any other symptom patient reported]?"
7.0	**Study Experiences**	**Code any symptom improvement mentioned (no matter how slight) and description of improvement.**
7.1	Overall impressions of the study drug	Code response to question "What were your overall impressions of the study drug?"
7.2	Improve_Numbness	Neuropathic pain described as numbness or dead feeling
7.3	Improve_Tingling	Neuropathic pain described as tingling or pins and needles
7.4	Improve_Weakness	Neuropathic pain described as weakness
7.5	Improve_Sensitivitiy	Neuropathic pain described as very sensitive or sensitivity to touch and pressure
7.6	Improve_Other	Any other descriptions of neuropathic pain
7.12	No_Improvement	If the study participants reported no improvements in symptoms during the clinical trial
7.13	Noticed improvements	Code response to question "How soon after receiving the study drug did you notice these improvements" and all related probes

Code		Operational Definition
8.0	**Importance of Symptom Improvement**	**These codes are participant's responses to importance rating of each symptom improvement from interview guide. Code entire response.**
8.1	Why_Important	Code entire importance rating, why
8.2	Most Important Improvement	Response to the following question: "Thinking about the improvements you noticed as a result of study drug, which are the most important? Why?"
9.0	**Impact of Improvement**	**Code any reports of improvements/reductions in the impact of their DPNP due to improvements in symptoms during study treatment**
9.1	Tx_Impact_daily activities_work	Impact on any gainful activities (e.g., absenteeism, productivity)
9.2	Tx_Impact_daily activities_home	Impact on activities completed at home (running a household, caring for family)
9.3	Tx_Impact_mobility	Impact on walking, using stairs, getting up/down from a chair or toilet, etc.
9.4	Tx_Impact_mood/emotions	Impact on mood/emotions/feelings, such as depressed mood, anxiety, irritability, anger
9.5	Tx_Impact_self-care	Impact on ability to engage in self-care activities such as bathing, dressing, using utensils
9.6	Tx_Impact_sleep	Impact on ability to get to sleep or stay asleep
9.7	Tx_Impact_most bothersome	Treatment improvement (if any) on symptom or impact reported as most bothersome
10.0	**Treatment Satisfaction and Preference**	
10.1	Study treatment satisfaction	Response to question "Overall, how satisfied are you with the study drug as a treatment for diabetic neuropathic pain? Why?"
10.2	Treatment preference	Response to question "Thinking about the study drug compared to the neuropathic pain treatment(s) you had tried before the study, which did you prefer? Why?"
10.3	Continue treatment	Response to "Would you have continued taking the study drug if you could have? Why?"

Appendix C. Anticipated Table Shells for Final Report

Table C-1. Demographic and Clinical Characteristics by Treatment Group

Characteristic	LX9211 10 mg	LX9211 20 mg	LX9211 All	Placebo	Total
Gender					
Male, n (%)					
Female, n (%)					
Age, mean (range)					
Age at diabetes diagnosis, mean (range)					
Age at onset of DPNP symptoms, mean (range)					
Mean baseline ADPS Score (range)					
Mean change in ADPS (range)					

ADPS = average daily pain score; DPNP = diabetic peripheral neuropathy pain.
ADPS is rated on a 0-10 numeric rating scale where 0 = no pain and 10 = worst imaginable pain.

Table C-2. Frequency of DPNP Symptoms Reported by Treatment Group

Symptom	LX9211 10 mg, n (%)	LX9211 20 mg, n (%)	LX9211 All, n (%)	Placebo, n (%)	Total, n (%)
Symptom 1					
Symptom 2					
Symptom 3					
Symptom 4					

Table C-3. Location of Neuropathic Pain Reported by Treatment Group

Location of Pain	LX9211 10 mg, n (%)	LX9211 20 mg, n (%)	LX9211 All, n (%)	Placebo, n (%)	Total, n (%)
Location 1					
Location 2					
Location 3					
Location 4					

Table C-4. Location with Most Severe Pain by Treatment Group

Location of Pain	LX9211 10 mg, n (%)	LX9211 20 mg, n (%)	LX9211 All, n (%)	Placebo, n (%)	Total, n (%)
Location 1					
Location 2					
Location 3					
Location 4					

Table C-5. Difficulty Managing Neuropathic Pain Before Clinical Trial by Treatment Group

Treatment Group	0 (Not all difficult) n (%)	1 (A little difficult) n (%)	2 (Moderately difficult) n (%)	3 (Quite difficult) n (%)	4 (Very difficult) n (%)	Mean (SD), n Median, Min:Max
Overall						
LX9211 All						
LX9211 10 mg						
LX9211 20 mg						
Placebo						

Table C-6. Frequency of DPNP Impacts Before the Clinical Trial by Treatment Group

Impact	LX9211 10 mg, n (%)	LX9211 20 mg, n (%)	LX9211 All, n (%)	Placebo, n (%)	Total, n (%)
Impact 1					
Impact 2					
Impact 3					
Impact 4					

Table C-7. Most Bothersome Symptom Before the Clinical Trial by Treatment Group

Symptom	LX9211 10 mg, n (%)	LX9211 20 mg, n (%)	LX9211 All, n (%)	Placebo, n (%)	Total, n (%)
Symptom 1					
Symptom 2					
Symptom 3					
Symptom 4					

Table C-8. Frequency of Symptoms Patients Most Wanted to See Treated in Clinical Trial by Treatment Group

Symptom	LX9211 10 mg, n (%)	LX9211 20 mg, n (%)	LX9211 All, n (%)	Placebo, n (%)	Total, n (%)
Symptom 1					
Symptom 2					
Symptom 3					
Symptom 4					

Table C-9. Importance of Symptoms Patients Most Wanted to See Treated by Treatment Group

	Placebo		LX9211 10 mg		LX9211 20 mg		LX9211 All	
Symptom	Importance Rating[a] Mean (Min to Max), n	Frequency of 'Very' or 'Extremely' Important Rating n (%)	Importance Rating[a] Mean (Min to Max), n	Frequency of 'Very' or 'Extremely' Important Rating n (%)	Importance Rating[a] Mean (Min to Max), n	Frequency of 'Very' or 'Extremely' Important Rating n (%)	Importance Rating[a] Mean (Min to Max), n	Frequency of 'Very' or 'Extremely' Important Rating n (%)
Symptom 1								
Symptom 2								
Symptom 3								
Symptom 4								

[a] Rating scale:1 = Not at all important, 2 = A little important, 3 = Somewhat important, 4 = Very important, 5 = Extremely important.

Table C-10. Frequency of Reported Symptom Improvement by Treatment Group

Symptom	LX9211 10 mg, n (%)	LX9211 20 mg, n (%)	LX9211 All, n (%)	Placebo, n (%)	Total, n (%)
Symptom 1					
Symptom 2					
Symptom 3					
Symptom 4					

Table C-11. Symptom Improvement Importance Ratings by Treatment Group

	Placebo		LX9211 10 mg		LX9211 20 mg		LX9211 All	
Symptom	**Importance Rating[a] Mean (Min to Max), n**	**Frequency of 'Very' or 'Extremely' Important Rating n (%)**	**Importance Rating[a] Mean (Min to Max), n**	**Frequency of 'Very' or 'Extremely' Important Rating n (%)**	**Importance Rating[a] Mean (Min to Max), n**	**Frequency of 'Very' or 'Extremely' Important Rating n (%)**	**Importance Rating[a] Mean (Min to Max), n**	**Frequency of 'Very' or 'Extremely' Important Rating n (%)**
Symptom 1								
Symptom 2								
Symptom 3								
Symptom 4								

[a] Rating scale:1 = Not at all important, 2 = A little important, 3 = Somewhat important, 4 = Very important, 5 = Extremely important

Table C-12. Frequency of Improvement in DPNP Impacts by Treatment Group

Impact	LX9211 10 mg, n (%)	LX9211 20 mg, n (%)	LX9211 All, n (%)	Placebo, n (%)	Total, n (%)
Impact 1					
Impact 2					
Impact 3					
Impact 4					

Table C-13. Satisfaction With DPNP Treatment Before Clinical Trial by Treatment Group

Treatment Group	0 (Not at all satisfied) n (%)	1 (A little satisfied) n (%)	2 (Moderately satisfied) n (%)	3 (Quite satisfied) n (%)	4 (Very satisfied) n (%)	Mean (SD), n Median, Min:Max
Overall						
LX9211 All						
LX9211 10 mg						
LX9211 20 mg						
Placebo						

DPNP = diabetic peripheral neuropathic pain; SD = standard deviation.

Table C-14. Baseline ADPS by Satisfaction with Previous DPNP Treatment at Baseline

Treatment Group	0 (Not at all satisfied) n (%)	1 (A little satisfied) n (%)	2 (Moderately satisfied) n (%)	3 (Quite satisfied) n (%)	4 (Very satisfied) n (%)
Overall					
n (%)					
Mean, Median (SD)					
Min-Max					
LX9211 All					
n (%)					
Mean, Median (SD)					
Min-Max					
LX9211 10 mg					
n (%)					
Mean, Median (SD)					
Min-Max					
LX9211 20 mg					
n (%)					
Mean, Median (SD)					
Min-Max					
Placebo					
n (%)					
Mean, Median (SD)					
Min-Max					

ADPS = average daily pain score; DPNP = diabetic peripheral neuropathic pain; SD = standard deviation.
Correlation between Satisfaction with previous DPNP treatment and baseline ADPS: r = 0.xx; n = xx

Table C-15. Study Drug Treatment Satisfaction at End of Treatment by Treatment Group

Treatment Group	0 (Not at all satisfied) n (%)	1 (A little satisfied) n (%)	2 (Moderately satisfied) n (%)	3 (Quite satisfied) n (%)	4 (Very satisfied) n (%)
Overall					
LX9211 All					
LX9211 10 mg					
LX9211 20 mg					
Placebo					

Table C-16. Change from Baseline in ADPS by Study Drug Treatment Satisfaction at End of Treatment

Treatment Group	0 (Not at all satisfied) n (%)	1 (A little satisfied) n (%)	2 (Moderately satisfied) n (%)	3 (Quite satisfied) n (%)	4 (Very satisfied) n (%)
Overall					
n (%)					
Mean, Median (SD)					
Min-Max					
LX9211 10 mg					
n (%)					
Mean, Median (SD)					
Min-Max					
LX9211 20 mg					
n (%)					
Mean, Median (SD)					
Min-Max					
Placebo					
n (%)					
Mean, Median (SD)					
Min-Max					

ADPS = average daily pain score; SD = standard deviation.

Correlation between Satisfaction with study drug and change from baseline ADPS: r = 0.xx; n = xx

Table C-17. Treatment Preference by Treatment Group

Preference	LX9211 10 mg, n (%)	LX9211 20 mg, n (%)	LX9211 All, n (%)	Placebo, n (%)	Total, n (%)
Study drug					
Previous DPNP medication					

DPNP = diabetic peripheral neuropathic pain.

Table C-18. Change from Baseline in ADPS and Treatment Preference

Preference	Study Drug	Previous DPNP Medication
Overall		
n (%)		
Mean, Median (SD)		
Min-Max		
LX9211 All		
n (%)		
Mean, Median (SD)		
Min-Max		
LX9211 10 mg		
n (%)		
Mean, Median (SD)		
Min-Max		
LX9211 20 mg		
n (%)		
Mean, Median (SD)		
Min-Max		
Placebo		
n (%)		
Mean, Median (SD)		
Min-Max		

ADPS = average daily pain score; SD = standard deviation.

Table C-19. Desire to Continue Study Drug by Treatment Group

Would Choose to Continue Study Drug	LX9211 10 mg n (%)	LX9211 20 mg, n (%)	LX9211 All, n (%)	Placebo n (%)	Total n (%)
Yes					
No					

Table C-20. Change from Baseline in ADPS and Desire to Continue Study Drug

Would Choose to Continue Study Drug	Yes	No
Overall		
n (%)		
Mean, Median (SD)		
Min-Max		
LX9211 All		
n (%)		
Mean, Median (SD)		
Min-Max		
LX9211 10 mg		
n (%)		
Mean, Median (SD)		
Min-Max		
LX9211 20 mg		
n (%)		
Mean, Median (SD)		
Min-Max		
Placebo		
n (%)		
Mean, Median (SD)		
Min-Max		

ADPS = average daily pain score; SD = standard deviation.