Official Title: A Phase 2, Double-blind, Randomized, Placebo controlled, Parallel-group Study to Evaluate the Efficacy and Safety of LX9211 in the Treatment of Postherpetic Neuralgia (RELIEF-PHN1)

NCT Number: NCT04662281

Document Date: Statiscal Analysis Plan Version 3: 28-November-2022

16.1.9 Documentation of statistical methods

Statistical Analysis Plan Final Version 3 – Dated 28 Novemeber 2022

Statistical Analysis Plan

Lexicon Pharmaceuticals, Inc.

Protocol No.: LX9211.1.202-PHN

A Phase 2, Double-blind, Randomized, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of LX9211 in the Treatment of Postherpetic Neuralgia (RELIEF-PHN1)

[redacted]

Document Version: Final v3.0
Document Date: 28-NOV-2022

Labcorp CDCS
Clinical Development Commercialization Services

Table of Contents

Reviewers

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

Name and Title	Role	Version Last Reviewed	Company/ Organization
[redacted]	[redacted]	3.0	[redacted]
[redacted]	[redacted]	3.0	[redacted]
[redacted]	[redacted]	1.0	[redacted]
[redacted]	[redacted]	3.0	[redacted]
[redacted]	[redacted]	2.0	[redacted]
[redacted]	[redacted]	3.0	Lexicon
[redacted]	[redacted]	3.0	Lexicon
[redacted]	[redacted]	3.0	Lexicon
[redacted]	[redacted]	2.0	Lexicon

Glossary of Abbreviations

Abbreviation	Term
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
BUN	blood urea nitrogen
CBC	complete blood count
C_{p2hr}	2-hr plasma concentrations
C_{trough}	trough plasma concentrations
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CPK	creatinine phosphokinase
DMC	Data Monitoring Committee
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 method
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
NRS	numerical rating scale
OC	observed cases
PGIC	Patient Global Impression of Change
PE	physical examination
PHN	postherpetic neuralgia
PK	pharmacokinetic(s)
PMM	pattern-mixture model
PP	Per Protocol
PRO	patient-reported outcomes

PT	Preferred Term
QTcF	Fridericia corrected QT
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
WHO	World Health Organization
ZBPI	Zoster Brief Pain Inventory

1. Source Documents

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

Document	Date	Version
Protocol	14 September 2020	Final
Protocol Amendment	23 October 2020	1
Protocol Amendment	03 March 2021	2
Protocol Amendment	15 April 2021	2.1
Protocol Amendment	15 October 2021	3
Electronic case report form (eCRF)	02 December 2020	Final

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 postherpetic neuralgia (PHN).

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 during, and following, the Week 6 double-blind Treatment Period.

2.1.3 Other Objective(s)

Other objectives (endpoints) of this study are:

- Change from Baseline to Week 6 in the Neuropathic Pain Symptom Inventory (NPSI)
- Change from Baseline to each week in the average daily pain score (ADPS), based on Question 5 of the Zoster Brief Pain Inventory (ZBPI)
- Proportion of patients with ≥30% reduction from Baseline in ADPS, based on Question 5 of the ZBPI by week
- Proportion of patients with ≥50% reduction from Baseline in ADPS, based on Question 5 of the ZBPI by week
- Cumulative distribution function of percent change in ADPS based on Question 5 of the ZBPI from Baseline to Week 6 comparing the LX9211 treatment group to placebo

- Cumulative distribution function of percent change in ADPS based on Question 5 of the ZBPI from Week 6 to Week 11 comparing the LX9211 treatment group to placebo
- To evaluate plasma levels of LX9211 in patients with PHN.
- 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 PHN.

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 or female patients ≥18 years of age, with prior herpes zoster skin rash and PHN pain persisting for ≥3 months after healing of the herpes zoster skin rash who meet all inclusion and no exclusion criteria are eligible for enrollment.

Eligible patients may continue use of 1 medication prescribed for PHN including pregabalin, gabapentin, and tricyclic antidepressant medications, as long as they have been at stable doses for ≥1 month prior to Screening and are willing to maintain their doses for the duration of the study. Patients taking more than 1 permitted concomitant medication for the treatment of PHN and unable to washout of all but 1 of these treatments for the duration of the study are not eligible. Use of any new medications, prescribed or over-the-counter for treatment of PHN pain, is not permitted during the course of the study. Use of any opioid medications for the management of PHN within the 2 months prior to Screening is not permitted. Brief use (<1 week) of opioid medication for management of non-PHN acute pain ≥2 months prior to the Screening Visit is permitted.

Screening Period: After signing the Informed Consent Form (ICF), all patients will enter a Screening Period of up to 2 weeks. Patients using non-opioid medications that are prohibited by the protocol must discontinue or washout these medications as directed by the protocol prior to entering the Screening period. 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 remaining duration of the Run-in Period, patients will take a single tablet of study drug every morning. Each evening patients will rate and record the intensity of their PHN pain based on Question 5 of the ZBPI by answering the question "Please rate your pain by indicating the one number that best describes your pain on the average in the

last 24 hours", on the 11-point numerical rating scale (0 [No Pain] to 10 [Pain as bad as you can imagine]). The ADPS will be calculated using all available daily pain diary data. The mean value of the ADPS derived over Week 2 will serve as the Baseline measure used for analyses. In order to qualify for randomization, patients must complete ≥70% of the daily pain diary entries during the second week of the Run-in Phase, 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 due to laboratory values may have those assessments repeated and be rescreened once after discussion with the Sponsor's 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 the 6-week double-blind Treatment Period. Patients will be randomly assigned in a 1:1 ratio between the following 2 treatment groups:

- **Group 1:** LX9211 200 mg* / 20 mg**, once daily (qd)
- **Group 2:** Placebo, qd matching loading and maintenance doses

* Loading dose (Day 1)

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

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

On Day 1, patients will be assigned to LX9211 or placebo, 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, orthostatic vital signs will be obtained (heart rate and blood pressure) after which time patients may be released and a 2-hour postdose blood draw will occur.

The loading dose will be followed by a daily maintenance dose taken at home in the morning 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 their average daily severity of their PHN over the previous 24 hours using Question 5 of ZBPI, record the use of rescue medication (acetaminophen), and rate the interference with sleep using Question 9F of the ZBPI. The ADPS will be calculated using all available data, however, a minimum of 4 days (consecutive or nonconsecutive) from the last week prior to each clinic visit is required for the calculation.

On the day of randomization, patients will also receive a bottle of acetaminophen. If a patient is unable to tolerate their PHN, 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 who discontinue prior to completion of the Week 6 Visit will not be replaced.

Patients discontinuing the study prior to completion of the Week 6 Visit should be encouraged to return for the Week 6 Visit assessments and complete the Safety Follow-up Visit 5 weeks later.

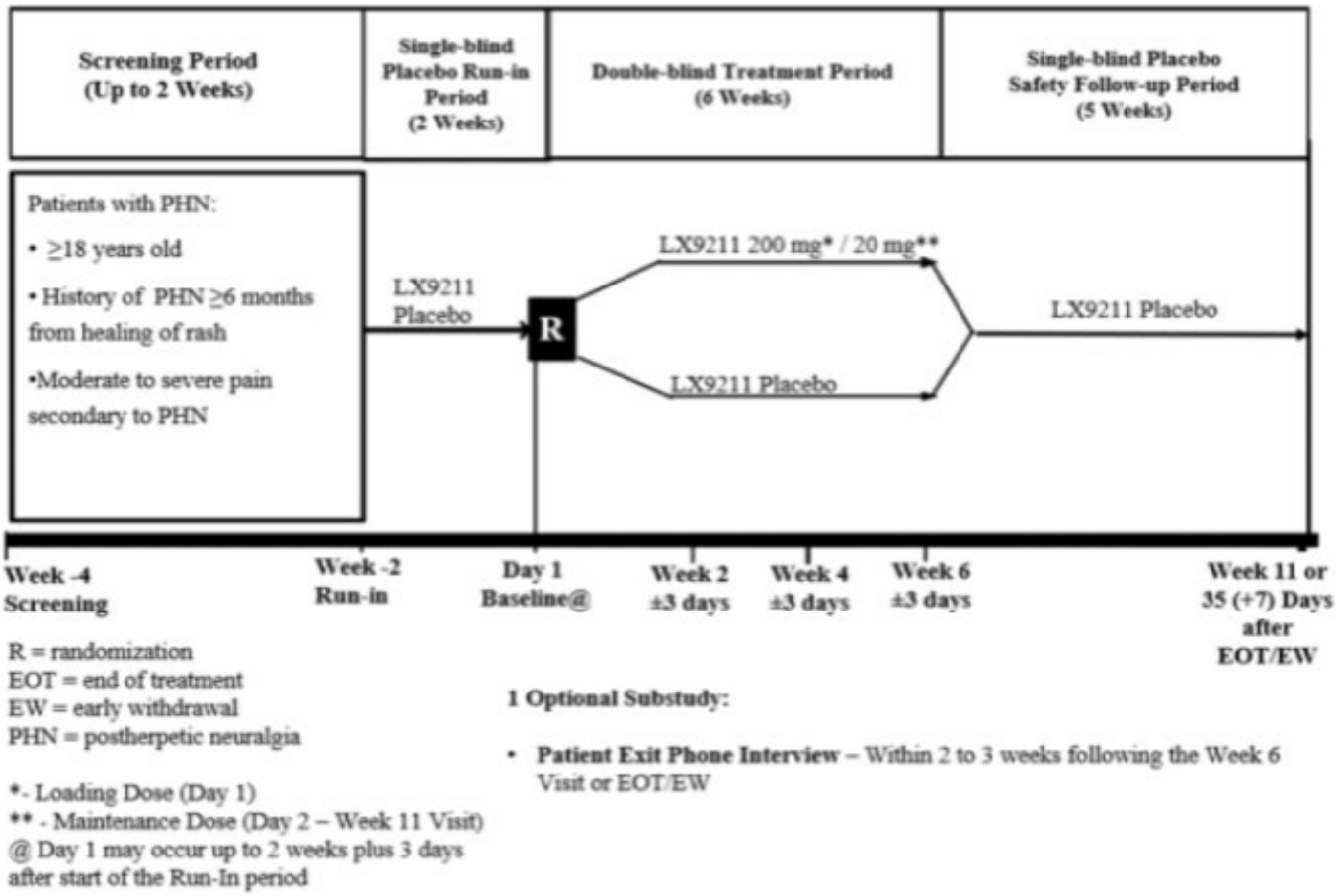
Safety Follow-up Period: Following completion of the 6-week double-blind Treatment Period, all patients will enter the 5-week single-blind Safety Follow-up Period. During this period, patients will dose with 1 tablet of single-blind study drug every morning taken at home. Each evening patients will continue to rate and record the average severity of their PHN over the previous 24 hours using Question 5 of the ZBPI, record the use of rescue medication (acetaminophen), and rate the interference with sleep using the ZBPI.

Blood samples for the determination of plasma LX9211 trough levels (C_{trough}) will be drawn predose on Day 1 and at Weeks 2, 4, 6, and 11. Blood samples will be drawn 2 hours after dosing on Day 1 for the determination of plasma 2-hour levels (C_{p2hr}).

[redacted]

Optional Substudy: During the Screening Visit, patients may choose to participate in an optional substudy. The optional substudy is a qualitative patient interview, which will include approximately 30 patients. The interview will be conducted over the telephone and is designed to gain insight and understanding of patients' experiences with symptoms of PHN 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

The proposed sample size is derived by satisfying the original design assumptions made for the primary efficacy endpoint. It is assumed that the difference in treatment group means is 0 under the null hypothesis (H_0) and is unequal to 0 under the alternative hypothesis (H_1); a 2-sided hypothesis under test. Under the H_1, the difference in group means of LX9211 minus placebo is expected to be -0.8 units with a common standard deviation (SD) of 1.0 units. These assumptions yield an effect size of 0.8. The effect size is the absolute value of the difference in treatment group means divided by the common SD of that difference. A uniform dropout rate of 0.15 is anticipated, and adjustment of the effect size for this rate results in an estimate 0.68; the adjusted difference in group means is equal to -0.8 units x 0.85 = -0.68. For a 2-sided test sized at $\alpha = 0.05$, 37 patients per treatment group are required under a 1:1 randomization ratio to detect the stated treatment difference under H1 with statistical power equal to 82.27% under a single stage design. The total planned N = 74 patients.

This study is designed as a group sequential trial with 1 interim look at the 50% information time point and a final analysis at 100%. A non-binding futility boundary will be used to test for futility of the primary endpoint. The futility boundary is 1-

sided with α = 0.025 and for the parameters specified, a power estimate of 82.53% is derived.

Sample Size Reestimation

Due to the uncertainty in the outcome for the primary endpoint analysis in this population, an unblinded SSR adaptation will be implemented at the time of the futility interim analysis. This will occur when the first 38 patients (rounded up from 37) 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 2 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 82.53% (the original specified power). 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, input a value for the maximum total number of patients (E[Max]) equal to 148 patients and, specify a reestimation rule as the Exact E method. The Exact E method increases the patient number total until the desired conditional power is achieved.

[redacted]

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 ZBPI, the 11-point numerical rating scale (0 [No Pain] to 10 [Pain as bad as you can imagine]) of LX9211 compared to placebo.

3.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are to be assessed in LX9211 compared to placebo for each of the following listed below:

- Change from Baseline to Week 6 in pain interfering with sleep based on Question 9F of the ZBPI "Indicate the one number that describes how, in the past 24-hours shingles pain has interfered with your: Sleep (0 [Does not interfere] to 10 [Completely interferes])."
- Proportion of patients with ≥30% reduction in pain intensity in ADPS based on Question 5 of the ZBPI from Baseline to Week 6
- Proportion of patients with ≥50% reduction in pain intensity in ADPS based on Question 5 of the ZBPI from Baseline to Week 6
- Change from Baseline to Week 6 in interference in General Activity, Mood, Walking Ability, Normal Work (includes both outside the home and housework), Relations with other people, Sleep, and Enjoyment of Life interference based on the Questions 9A-G of the ZBPI
- Proportion of patients discontinuing treatment due to lack of efficacy defined as increase in ADPS from Baseline of ≥30% based on Question 5 of the ZBPI
- Patient Global Impression of Change (PGIC) at Week 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 ZBPI at Week 6

3.3 Other Efficacy Endpoints

The other efficacy endpoints are to be assessed in LX9211 compared to placebo for each of the following 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 ZBPI
- Proportion of patients with ≥30% reduction from Baseline in ADPS, based on Question 5 of the ZBPI by week
- Proportion of patients with ≥50% reduction from Baseline in ADPS, based on Question 5 of the ZBPI by week
- Cumulative distribution function of percent change in ADPS based on Question 5 of the ZBPI from Baseline to Week 6 comparing each LX9211 treatment group to placebo
- Cumulative distribution function of percent change in ADPS based on Question 5 of the ZBPI from Week 6 to Week 11 comparing the LX9211 treatment group to placebo

3.4 Safety Variables

Safety endpoints are as follows:

- Incidence of treatment-emergent AEs (TEAEs), suspected adverse reaction, AEs leading to discontinuation from the study, serious AEs (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) /Pharmacodynamic (PD) Variables

The PK endpoints are the plasma C_{p2hr} and C_{trough} levels of LX9211 in patients with postherpetic neuralgia.

[redacted]

5. Analysis Populations

Analysis of the primary, secondary and other 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 Population

The mITT population will include all randomized patients who take at least 1 dose of study drug during the double-blind Treatment Period. 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 patient'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 [redacted] 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 4 or Exclusion Criterion 4 or 7, which are 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	Patients who received a wrong	**Programmatic** check based on

Treatment Allocation	treatment at 1 or more study visits due to packaging or dispensing errors during the double-blind Treatment Period	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	[redacted] 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, Inc. prior to database lock and 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 Population

The PK population for evaluation of C_{p2hr} and C_{trough} will include all randomized patients who received at least 1 dose of study drug during the double-blind Treatment Period and had at least 1 sample collected.

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, defined as the 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 time point windows defined in Table 1.1 will be used for the analyses of the primary efficacy endpoint, the secondary efficacy endpoints, 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 ZBPI 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 ZBPI is defined as the value collected at the time of the clinic visit on Day 1 but prior to intake of the first dose of study drug. As a sensitivity analysis, the mean value of Question 9F of the ZBPI of daily diary over Week 2 of the single-blind Run-in Period will be used as the Baseline, 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 ZBPI, 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
Week 2	Day 15	Days 2 to 22 (Day 15-13 days, Day 15+7 days)
Week 4	Day 29	Days 23 to 36 (Day 29-6 days, Day 29+7 days)
Week 6	Day 43	Days 37 to 60 (Day 43-6 days, Day 43+17 days)
Week 11	Day 78	Day 61 to 40 days after the last treatment dose during the double-blind Treatment Period (≥ Day 78-17 days, last treatment dose + 40 days)

[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 as 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 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.

The Hospital Anxiety and Depression Scale (HADS) is collected only at Screening and imputation of missing data is 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): whether data is missing 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	LX9211 200 mg/20 mg Placebo Total (if applicable)
Tables	Data in summary tables presented by treatment group, assessment (where applicable) and visit (where applicable)
Listings	All data collected presented by treatment group, site, patient, and visit (where applicable), date, unless otherwise specified

Principle	Value
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 per treatment group 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
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 qualitative patient interview substudy
- Completed single-blind Safety Follow-up Period
- Discontinued single-blind Safety Follow-up Period
- Included in each study population (ITT, mITT, PP, PK 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, respectively.

A summary of patient enrollment by site will 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 ZBPI, 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 treatment group and overall 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)
- Baseline postherpetic neuralgia (PHN) 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 with 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 derived 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, exploratory analyses will be performed on the PP population.

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. Unadjusted p-values will be presented for all analysis results.

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 ZBPI, the 11-point numerical rating 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 ZBPI, 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, i.e.

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 ZBPI 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 the Baseline ADPS score as a covariate. An unstructured covariance structure will be used to model the within-patient error. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Other covariance structures will be explored should convergence not be met.

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 LX9211 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 LX9211 versus placebo for the change from Baseline scores. Tabulation of the inferential results (CIs and p-values) will include the observed findings 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 weeks as well as LS mean change by weeks, 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: ZBPI 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 the 11-point numerical rating scale (NRS) 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 ZBPI 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 Change from Baseline to Week 6 in pain interfering with sleep based on Question 9F of the ZBPI

The change from Baseline to Week 6 in pain interference with sleep based on Question 9F of the ZBPI "Indicate the one number that describes how, in the past 24-hours shingles pain has interfered with your: Sleep (0 [Does not interfere] to 10 [Completely interferes])", 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 ZBPI 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 ZBPI, 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.

7.6.2.2 Proportion of patients with ≥30% reduction in pain intensity in ADPS based on Question 5 of ZBPI 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 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.

7.6.2.3 Proportion of patients with ≥50% reduction in pain intensity in ADPS based on Question 5 of ZBPI 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 7.6.2.2.

7.6.2.4 Change from Baseline to Week 6 based on the Questions 9A-G of the ZBPI

The ZBPI is a patient-reported outcome (PRO) assessed on a validated electronic device completed at the time of the clinic visit. The ZBPI, a 9-item questionnaire assesses the severity of pain and its impact on functioning in patients with PHN.

The following pain interference categories based on Questions 9A-G of the ZBPI, completed at the time of the clinic visit, will be analyzed separately:

- General activity
- Mood
- Walking ability
- Normal work
- Relations with other people

- Sleep
- Enjoyment of life

The change from Baseline to Week 6 in 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.

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, along with their 95% CIs and p-value will be presented.

7.6.3 Sensitivity Analyses

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 to 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 group 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 with 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.

Another sensitivity analysis will be performed for the weekly sleep score, which is the average of the daily score by week through Week 6. The baseline is the Week 2 sleep score from the Run-in period. The change from baseline to Week 6 will be analyzed by using a similar MMRM method as the primary endpoint.

In the case there are patients with PK anomalies, eg, LX9211 randomized patients with $C_{trough}=0$ during double-blind phase, sensitivity analyses will be performed excluding these patients from the primary analysis model for the primary endpoint at Week 6.

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
- Baseline PHN drug use, yes or no
- Subjects who experience the 5 specific TEAEs, yes or no

Baseline PHN drug use subgroup is defined as those who took concomitant PHN 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 all efficacy endpoints will be presented by treatment group and by study visit/week across double-blind Treatment Period and single-

blind Safety Follow-up period. 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 LX9211 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 of Question 5 of the ZBPI 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 ZBPI, 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 (ie, Weeks 2, 4, and 6) 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 ZBPI 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 ZBPI 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 ZBPI 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 ZBPI 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 ZBPI 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 ZBPI 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 ZBPI 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 ZBPI 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.

7.6.6 PK/PD

C_{trough} values will be summarized at Weeks 2, 4, 6, and 11. C_{p2hr} values will be summarized on Day 1, using descriptive statistics by treatment group.

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, regardless of unplanned intermittent discontinuations:

(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-blind 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 PHN drug use, by PT
- The five Specific TEAEs and age category (<50, 50-65, 66-75, and >75 years old), 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 time to onset and AE duration, the denominator for percentage is defined as the number of patients in each subgroup with the respective specific TEAEs in the double-blind treatment period for each treatment group. For the other subgroups,

the denominator for the percentage is defined as the number of patients in each category of a subgroup in 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 <u>Urine microscopy</u> 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 and weight

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.

7.7.5 Electrocardiograms

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)
- 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 analysis will occur when the first 38 patients have been accrued and followed to the 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. The patient number for the interim analysis has been rounded upward from 37 to 38 patients to yield the minimum number of patients exceeding the 50% information fraction that preserves the 1:1 randomization schema.

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 51.4% 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 an overall Type 1 error rate = 0.025 (or a two-sided α = 0.05). Use of this beta spending function for futility testing is conservative and results in cumulative beta error rates of 0.015 and 0.175 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). The trial may stop for futility due to test statistic being below -0.085 (futility bound (one-sided only)).

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 patent accrual (eg, 25% and 75% of the original sample size). DMC meetings planned after the interim analysis may be modified in their timing and frequency should the sample size be adjusted upward. A final DMC meeting is planned when the study completes. The DMC will develop a charter and establish criteria for 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.

Since the date and reasons for discontinuation at single-blind Safety Follow-up Period are not collected, the secondary endpoints of the proportion of patients

discontinuing treatment due to lack of efficacy, the time to loss of efficacy from Week 6 to Week 11 defined in Section 3.2 will not be analyzed.

9. Data Issues

Not applicable

10. References

Not applicable

11. Appendices

Appendix 1 - Document History

Document Version, Status, Date	Summary/Reason for Changes
Version 1.0, Final, 18 FEB 2021	Not applicable; the first version
Version 2.0, Final, 12 NOV 2021	Updated according to protocol amendment 3
Version 3.0, Final, 28 NOV 2022	Updated to include additional sensitivity analyses and subgroup analyses

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	+5
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						X
BMI calculation	X						X
Patient completes HADS	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	±5
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	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 Question 5 of ZBPI and other ePRO questions on e-diary		Ongoing					
Review patient daily e-diary			X	X	X	X	X
Patient completes the Zoster Brief Pain-Inventory (ZBPI), dispense/review			X	X	X	X	X
Patient completes PGIC						X	X
Patient completes NPSI			X			X	X
Laboratory Assessments							
Serum chemistry	X		X	X	X	X	X
Hematology	X		X			X	X
Urinalysis with microscopy	X		X	X	X	X	X
Pregnancy test (serum) [i]	X						
Pregnancy test (urine) [i]	X		X			X	
FSH (females only) [j]	X						

Urine drug test for drugs of abuse and cannabinoids	X		X				
C_{p2hr} and C_{trough} blood samples [k]			X (pre and 2 hr post-dose)	X	X	X	X
[redacted]							
Exit Interview Substudy Assessments							
Exit interview [l]						X	

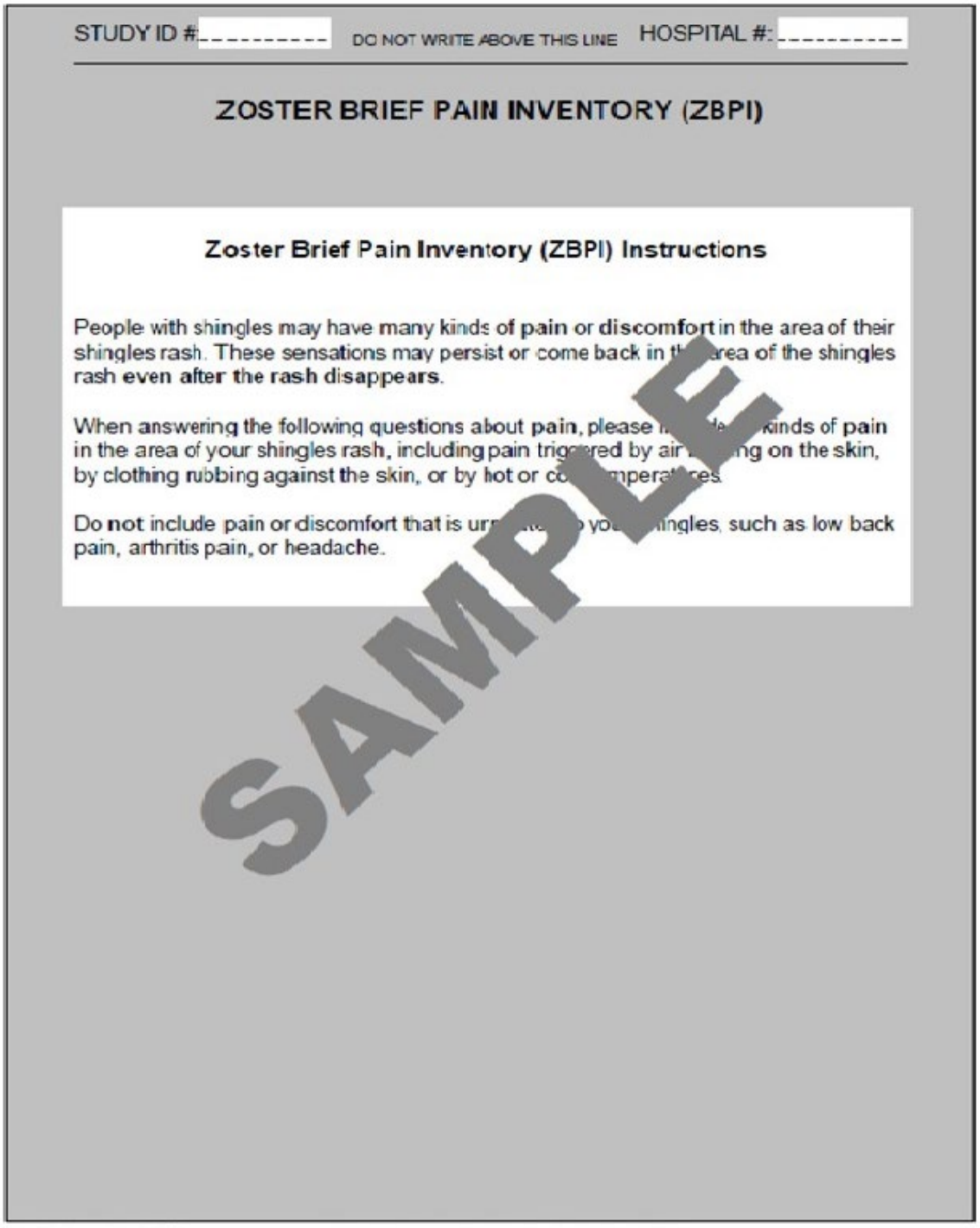
Abbreviations: A1C = hemoglobin A1C; AE = adverse event; BMI = body mass index; ECG = electrocardiogram; FSH = follicle-stimulating hormone; GFR = glomerular filtration rate; PK = pharmacokinetics; SAE = serious adverse event; IXRS = Interactive Voice/Web Response System; HADS = Hospital Anxiety and Depression Scale; PGIC = Patient Global Impression of Change; ZBPI = Zoster Brief Pain Inventory

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 examination will only occur if the patient is experiencing symptoms or AEs. If a symptom-related brief physical examination is required, it should include a review of all body systems that relate to the symptoms and/or AE(s) that the patient is experiencing.
d. Orthostatic vitals will be collected at the Day 1 Visit, 2 hours postdose 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 ≥30 minutes after phlebotomy.
f. The subject's use of concomitant medications will be captured at the Screening Visit through the Week 11/EOT/EW visit.
g. All SAEs will be collected, starting with signing of informed consent and continuing 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. At Screening either urine or serum pregnancy test must be obtained. A positive urine test must be confirmed with a serum test to allow eligibility. The 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.

[redacted]

l. Qualitative patient interviews to be completed by an independent third-party vendor within 2 weeks following the Week 6 Visit or Early Withdrawal Visit.

Appendix 3 – Zoster Brief Pain Inventory (ZBPI)



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

ZOSTER BRIEF PAIN INVENTORY (ZBPI)

Zoster Brief Pain Inventory (ZBPI) Instructions

People with shingles may have many kinds of pain or discomfort in the area of their shingles rash. These sensations may persist or come back in the area of the shingles rash even after the rash disappears.

When answering the following questions about pain, please include all kinds of pain in the area of your shingles rash, including pain triggered by air touching on the skin, by clothing rubbing against the skin, or by hot or cold temperatures.

Do not include pain or discomfort that is unrelated to your shingles, such as low back pain, arthritis pain, or headache.

SAMPLE

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

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

ZOSTER BRIEF PAIN INVENTORY (ZBPI)

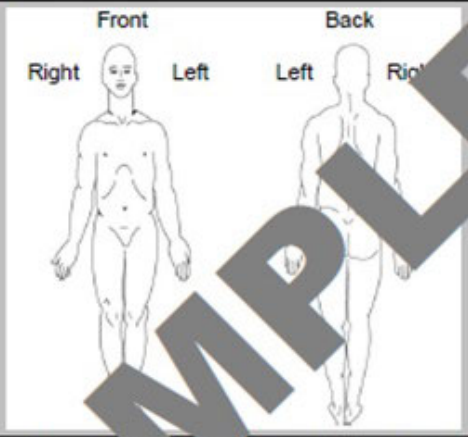
Date: ____/____/_____ **Time:** _____

Name: _____ _____ _____
Last First Middle Initial

1. Have you had any pain caused by your shingles in the last 24 hours?

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 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 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 by circling the one number that best describes your pain on the average 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

6. Please rate your pain 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

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

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

ZOSTER BRIEF PAIN INVENTORY

Date:____/____/_____ Time:_____

Name:_____ _____ _____
Last First Middle Initial

7. Are you receiving any treatments or medications for your shingles pain?

1. Yes 2. No

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

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

9. Circle the one number that describes how, in the last 24 hours, shingles pain 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

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Appendix 4 – Patient's Global Impression of Change (PGIC) Scale

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-C_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.

NPSI - United Kingdom/English - MAPI Institute.
ID6919 / NPSI_AU1.0_eng-GBen.doc

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

		A	D
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.

TOTAL | | |

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