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

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Lexicon

CLINICAL STUDY PROTOCOL

Protocol Number:	LX9211.1-202-PHN LX9211.202 (Abbreviated number)
EudraCT Number	2020-004639-26
Investigational Phase:	Phase 2
Protocol 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)
Amendment 3 Date:	15 October 2021
Amendment 2 Date:	03 March 2021
Amendment 1 Date:	23 October 2020
Original Version Date	14 September 2020
Sponsor:	Lexicon Pharmaceuticals, Inc. 2245 Technology Forest Blvd, Level 11 The Woodlands, TX 77381-5261 Telephone: (281) 863-3000 Safety Data Facsimile: (832) 442-5462
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Investigator Signature Page

Protocol Number:	LX9211.202
EudraCT Number:	2020-004639-26
Protocol 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)
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By my signature below, I hereby attest that I have read and that I understand and will abide by all the conditions, instructions, and restrictions contained in the attached protocol and will conduct the study in accordance with International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP) guidance.

Additionally, I will not initiate this study without written and dated approval from the appropriate Institutional Review Board (IRB)/Ethic Review Committee (ERC), and I understand that any changes in the protocol must be approved in writing by the Sponsor, the IRB/ERC, and, in certain cases the US Food and Drug Administration (FDA) or other applicable regulatory agencies, before they can be implemented, except where necessary to eliminate hazards to patients.

Principal Investigator's Signature	Date
Principal Investigator' Name (Print) DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 18-Oct-2021 | 1:56 PM CDT 53FB428455294E729D41E061C80A34CE	18-Oct-2021 | 1:57 PM CDT
Lexicon [redacted] (Signature)	Date
[redacted], MD	
Lexicon [redacted] (Printed Name)	

1. Synopsis

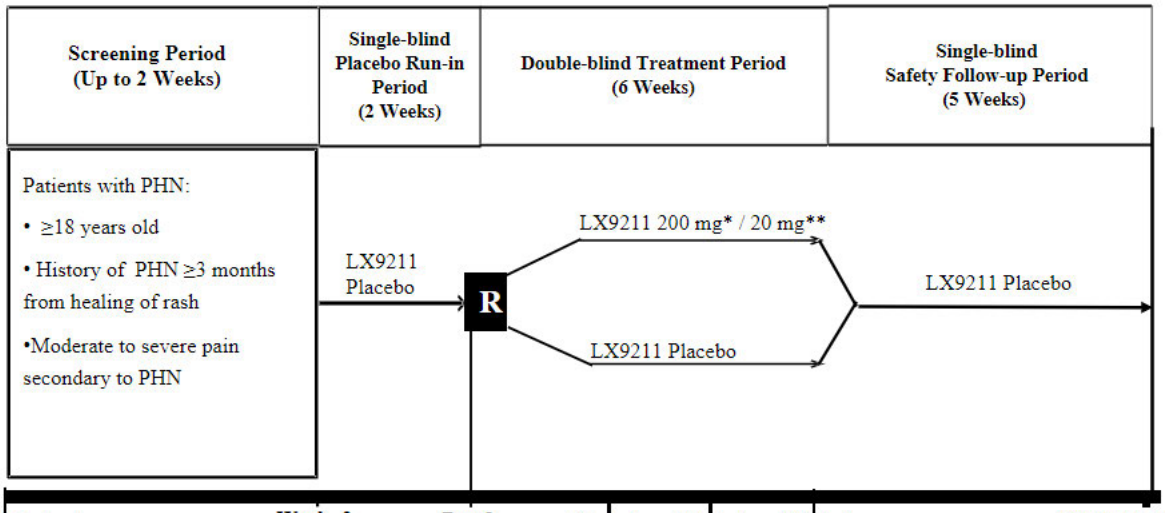
Name of Study Drug	LX9211 phosphate
Protocol Number	LX9211.1-202-PHN LX9211.202 (Abbreviated number)
Protocol Title	A Phase 2, Double-blind, Randomized, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of LX9211 in the Treatment of Postherpetic Neuralgia (RELIEF-PHN1)
Primary Objective	To evaluate the efficacy of LX9211 in reducing pain related to postherpetic neuralgia (PHN)
Primary Efficacy Endpoint	The change from Baseline (Week 2 of the Run-in Period) to Week 6 in Average Daily Pain Score (ADPS), based on Question 5 of the Zoster Brief Pain Inventory (ZBPI), the 11-point numerical rating scale (0 [No Pain] to 10 [Pain as bad as you can imagine])
Secondary Objectives	To assess other effects and patient reported outcomes of LX9211 versus placebo during and following the Week 6 double-blind Treatment Period
Secondary Efficacy Endpoints	• 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 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.

Other Efficacy Endpoints	• Change from Baseline to Week 6 in the Neuropathic Pain Symptom Inventory (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 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
Pharmacokinetic (PK) / Pharmacodynamic (PD) Objectives	To evaluate plasma levels of LX9211 in patients with PHN Blood samples will be collected from patients [redacted]
Safety Objectives	Safety will be assessed by adverse events (AEs), vital signs, electrocardiogram (ECG) findings, and laboratory parameters
Phase of Development	Phase 2
Methodology	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); 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 and older 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 (TCA) medications as long as they have been at stable doses for ≥1 month prior to Screening. Patients who are taking more than 1 permitted concomitant medication for the treatment of PHN and are 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 (OTC), 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. **Note:** Brief use (<1 week) of opioid medication for management of non-PHN acute pain (eg, tooth extraction/acute injury) ≥2 months prior to 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 of these medications for ≥2 weeks 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 in order to qualify that the criteria for moderate to severe pain are met and to demonstrate ≥80% compliance with taking the expected amount of placebo tablets. On Day 1 of the Run-in Period patients will be dispensed 4 tablets of single-blind placebo to be administered at the site. For the remainder of the Run-in Period, patients will take a single tablet of study drug every morning. Each evening patients will rate and record 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 have completed ≥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 use of any rescue medication. On the morning of the Run-in Visit, patients may eat 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 a 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 receive LX9211 or placebo, to be given as a loading dose at the clinic. The loading dose will be followed by a daily maintenance dose taken at home on Day 2 through end of Week 6. **Note:** On days of clinic visits, patients will refrain from taking their daily dose until after the visit. Each evening during the double-blind Treatment Period, patients will be required to rate and record the average severity of their PHN pain 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 Question 9F. 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. If a patient is unable to tolerate their PHN, they are encouraged to discuss treatment options with the Investigator. At the Investigator's discretion, the patient may be permitted to take acetaminophen (up to a maximum of 3 grams per day) as a rescue medication. Only the acetaminophen provided by the Sponsor as a rescue medicine may be used during the course of the study. The use of personally acquired acetaminophen is prohibited. 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. **Safety Follow-up Period**: Following the double-blind Treatment Period, all patients will enter a 5-week single-blind Safety Follow-up Period. During this period, patients will dose with 1 tablet of single-blind study drug (placebo) every morning, taken at home. Patients will remain blinded to the study drug being taken. Each evening patients will continue to rate and record the average severity of their PHN over the previous 24 hours using the

	Question 5 of 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 telephone interview is designed to gain insight and understanding of patients' experiences with symptoms of PHN and to assess relevance and clinical meaningfulness of symptom improvements (eg, reduction in pain) with LX9211 treatment. The overall study design is presented in the diagram below:



R = randomization
EOT = end of treatment
EW = early withdrawal
PHN = postherpetic neuralgia

*- Loading Dose (Day 1)
** - Maintenance Dose (Day 2 – Week 11 Visit)
@ Day 1 may occur up to 2 weeks plus 3 days after start of the Run-In period

1 Optional Substudy:

- **Patient Exit Phone Interview** – Within 2 to 3 weeks following the Week 6 Visit or EOT/EW

Number of Patients	The proposed sample size is 74 patients, 37 randomized to each treatment group. The sample size will be reassessed at a planned interim analysis. The interim analysis will occur when the first 38 patients have been accrued and followed to endpoint at Week 6. Based on this assessment, the sample size will be reestimated and can remain as originally proposed or increased. The maximum increase is limited to 148 patients. The interim analysis will allow for statistical testing of futility and should the prespecified futility boundary be crossed, and other data support a negative trial finding, consideration will be made to stop patient accrual. Approximately 30 patients will be recruited to participate in a qualitative patient interview substudy for English speaking patients in the United States (US) only.
Study Population	Male and female patients 18 years or older will be enrolled. Patients will have a diagnosis of postherpetic neuralgia defined as pain in the dermatomal distribution of an acute herpes zoster skin rash, persisting for ≥3 months from the healing of herpes zoster

	skin rash. Patients will have to meet pain criteria at the end of the Run-in Period.	
Number of Study Sites	Approximately 30 with the majority of sites located in the US and approximately 10 sites will be located in Europe	
Treatments	Each patient will be randomized to 1 of the following groups:	
Treatment Group	**Loading Dose (Day 1) ***	**Maintenance Dose (Day 2 to Week 6 / EOT/EW) ****
Group 1: LX9211 200 mg*/20 mg**	2 x 50-mg LX9211 tablets + 2 x 50-mg LX9211 tablets	1 x 20-mg LX9211 tablet, qd
Group 2: Placebo	2 x Placebo tablets + 2 x Placebo tablets	1 x Placebo tablet, qd
* Loading Dose (Day 1) ** Maintenance Dose (Day 2 – Week 6 Visit)		
Route of Administration	Oral	
Duration of Treatment	Patients will be treated with double-blind study drug for 6 weeks. Patient participation will be approximately 105 days, including a 2-week Screening Period, a 2-week single-blind Placebo Run-in Period, a 6-week double-blind Treatment Period, and a 5-week single-blind Safety Follow-up Period.	
Inclusion Criteria	Patients must meet **all** of the following criteria to be considered eligible to participate in the study. For patients not meeting eligibility requirements, the reason for exclusion must be recorded. **Note**: Patients who are not eligible because of laboratory result(s) may have the laboratory test(s) repeated **once** during the Screening Period, at the discretion of the Investigator, to determine eligibility: 1. Patient has given written informed consent to participate in the study in accordance with local regulations	

	2. Adult male or female patients ≥18 years of age at the Screening Visit: a. Females of childbearing potential must have a negative serum or urine pregnancy test prior to the start of study drug. In the case of positive urine pregnancy testing, a negative serum sample for pregnancy testing, to confirm that the patient is not pregnant, must be obtained prior to start of study. They must also agree to use adequate methods of contraception which include the following: condom with spermicidal gel, diaphragm with spermicidal gel, coil (intrauterine device), surgical sterilization, vasectomy, oral contraceptive pill, depo-progesterone injections, progesterone implant (ie, Implanon®), NuvaRing®, Ortho Evra® b. Nonsterile male patients with sexual partners of childbearing potential must agree to use adequate methods of contraception from Baseline through the Week 11 Visit 3. Presence of PHN pain that is present for ≥3 months after healing of herpes zoster skin rash affecting a single dermatome. Patients with more than 1 involved dermatome may also be included, provided the affected dermatomes are contiguous. 4. Moderate to severe pain as confirmed by average pain score using scores recorded in the pain diary in the 14 days prior to randomization (Run-in Period) 5. At least 80% compliance with dosing during the 2-week Run-in Period, and 70% compliance with completion of the daily diary during the second week of the Run-in Period 6. Willing to adhere to the prohibitions and restrictions specified in the protocol
Exclusion Criteria	Patients who meet **any** of the following criteria will be excluded from participating in the study: 1. Presence of other painful conditions that may confound assessment or self-evaluation of PHN: a. Patient should not have any other neurological disorder or conditions that can cause symptoms that may mimic peripheral neuropathy or that might confound assessment of PHN pain.

	b. Other causes of diffuse painful peripheral neuropathy such as: paraproteinemia, untreated hypothyroidism (previously treated hypothyroidism not excluded if treated and euthyroid for ≥6 months), vitamin B12 deficiency, neurologically-evident vasculitis, malignancy, amyloidosis, renal insufficiency, connective tissue disease (eg, Sjogren's, systemic lupus erythematosus), porphyria, complex regional pain syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, alcoholism, HIV, hepatitis, uremia, syphilis, myeloma, or other systemic disease associated with a secondary painful neuropathy should be excluded. c. Patient should not have had any exposure to drugs/toxic environmental agents known to cause neuropathy 2. Over the past year, met Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria for a major depressive episode, any active, significant psychiatric disorders (eg, neurocognitive disorder, anxiety disorder, psychosis, bipolar disorder), or a history of clinically significant drug or alcohol use disorder that would, in the Investigator's opinion, interfere with the assessment and evaluation of pain during the study 3. Mood and anxiety disorder scores defined by Hospital Anxiety and Depression Scale (HADS) ≥13 4. Suspected or likely diagnosis of trigeminal neuralgia 5. Use of opioid medications for management of PHN within the 2 months prior to the Screening Visit. **Note:** Brief use (<1 week) of opioid medication for management of non-PHN acute pain (eg, tooth extraction/acute injury) ≥2 months prior to the Screening Visit is permitted. 6. Use of NSAIDs for the specific treatment of PHN pain. 7. Use of more than 1 permitted concomitant medications for the treatment of PHN. **Note:** Patients may washout additional PHN medications ≥1 month prior to the Screening Visit to reach the 1 permitted medication 8. For non-opioid medications patient uses and is unwilling/unable to discontinue use of prohibited medications and therapies, (eg, benzodiazepines, dextromethorphan, herbal medications, mexiletine HCl, adenosine, topical analgesics including lidocaine and

	capsaicin), applied to the same area of the body affected by PHN pain, nerve blocks, acupuncture, or other medications indicated for neuropathic pain. A patient using any of these interventions for neuropathic pain must discontinue the medication ≥1 month prior to starting the Screening Period and for the duration of the study. **Note:** This exclusion criterion does not include analgesics that are not specifically prescribed for treatment of neuropathic pain (eg, nonsteroidal anti-inflammatory drugs [NSAIDs], aspirin, acetaminophen). In addition, patients who are prescribed antidepressants for a mental health disorder are eligible to participate as long as they do not meet Exclusion Criteria 2-3. 9. A positive urine drug test for drugs of abuse including cannabinoids. **Note:** Cannabidiol (CBD), if used for mood or sleep, is acceptable. If used for PHN it would be allowed if it is the only concomitant medication being taken for PHN. If not the only medication being taken for PHN, it should be withdrawn ≥1 month prior to Screening 10. Patient has hepatic impairment at Screening, defined as any of the following: aspartate aminotransferase (AST) >2X upper limit of the normal reference range (ULN), alanine aminotransferase (ALT) >2X ULN, serum total bilirubin (TB) >2X ULN. **Note**: If it is the opinion of the Investigator and the Medical Monitor that an increase in bilirubin is due to Gilbert's syndrome, then the patient may participate. 11. Patient has abnormal kidney function test (estimated glomerular filtration rate [eGFR] <60 mL/min as calculated using the Cockcroft-Gault equation) at Screening or renal dysfunction requiring hemodialysis 12. Patient has any of the following medical conditions or disorders: epilepsy or seizure disorder requiring treatment with antiepileptic drugs 13. Presence of clinically significant physical examination (PE) findings other than PHN, or laboratory or ECG findings that in the opinion of the Investigator, Medical Monitor, and/or the Sponsor, may interfere with any aspect of study conduct or interpretation of results including: a. any clinically significant abnormal heart rate or rhythm b. other ECG abnormalities that are clinically relevant

	c. BP >160/100 mm Hg or <90/50 mm Hg d. presence of risk factors for torsade de points (eg, family history of long QT syndrome; personal history of NYHA class III/IV heart failure or structural heart disease) 14. Receipt of any investigational agent within 30 days or 5 half-lives, whichever is longer, prior to Baseline/Randomization on Day 1 15. Receipt of any therapeutic protein, antibody/biologic- or antibody-based agents (eg, growth hormones or monoclonal antibodies) within 3 months prior to dosing on planned Day 1. **Note:** Preventative vaccines (eg, influenza, pneumococcal, Tdap), will be allowed if administered >7 days prior to dosing. Patients who have previously received the shingles vaccine, but subsequently develop PHN and meet all inclusion and exclusion criteria, are eligible to participate. 16. Prior exposure to LX9211 17. History of any serious adverse reaction or hypersensitivity to any inactive component of study drug, unless the reaction is deemed irrelevant to the study by the Investigator, Medical Monitor, and/or the Sponsor 18. Presence of any skin condition, such as ulcers, which could interfere with assessment of PHN 19. Existence of any postsurgical or medical condition that, in the judgment of the Investigator, Medical Monitor, and/or the Sponsor, might interfere with the absorption, distribution, metabolism, or excretion of LX9211, including bariatric surgery, cholecystectomy, or any other GI surgery, except appendectomy and hernia repair, which are acceptable 20. History of any major surgery within 3 months prior to Baseline or surgery that is anticipated to be performed during the study period 21. History of any active infection within 30 days prior to Baseline, if deemed clinically significant by the Investigator, Medical Monitor, and/or the Sponsor 22. Malignancy or active treatment for malignancy (ie, radiation or chemotherapy, including monoclonal antibodies) within 5 years prior to the Screening Visit. **Note:** Patients with squamous or basal cell carcinomas of the skin, carcinomas in situ of the cervix or uterus, ductal

	breast cancer in situ, resected low-grade prostate cancer, or other malignancies that, in the opinion of the Investigator and the Medical Monitor are considered cured, may participate. 23. Donation or loss of >500 mL of blood or blood product within 3 months prior to Baseline 24. Inability or difficulty swallowing whole tablets 25. Any other condition that compromises the ability of the patient to provide informed consent or to comply with the objectives and procedures of this protocol, as judged by the Investigator, Medical Monitor, and/or the Sponsor 26. Unable or unwilling to adhere to the requirements of the protocol, or communicate or cooperate with the Investigator and/or their staff for any reason 27. Patient refuses to participate in processes if established by the Sponsor, to minimize duplicate patients (Verified Clinical Trials) 28. Employees, or relatives of the Sponsor, Investigator or study center staff, with direct involvement in the proposed study or other studies under the discretion of the Investigator or study center 29. Patient is immunocompromised (eg, secondary to transplant or require active immunosuppressive drugs)
Statistical Methods	A proposed sample size of 74 randomized patients will yield 82.27% power to detect a true mean difference of -0.68 units between the LX9211 treatment group and placebo in the primary efficacy endpoint, assuming a common standard deviation of 1 unit and a 2-sided significance level of α=0.05. This derivation is adjusted for a uniform dropout rate of 15%, that patients will be randomly assigned to treatment in a 1:1 ratio, and for an interim analysis conducted after about half of the originally proposed sample size has been accrued and followed to endpoint. The sample size can be increased to a maximum of 148 patients based on a reestimation procedure performed at the planned interim analysis. Continuous variables will be summarized by the mean, standard deviation, median, minimum, and maximum values for all patients with non-missing data. Categorical variables will be summarized by their counts and associated percentages. All data will be provided in individual patient listings.

	Analysis of the primary and secondary efficacy endpoints will be based on the Modified Intent-to-Treat (mITT) Population, defined as all randomized patients who had taken ≥1 dose of study drug. Safety endpoints analyses will be based on the Safety Population, defined as those patients who received any exposure to study drug. A restricted maximum likelihood-based, mixed-effects model repeated measures (MMRM) approach will be used to assess the difference between LX9211 and placebo for the primary endpoint. The MMRM model will include fixed effects of treatment, week, treatment-by-week interaction, the randomization factor of Baseline pain severity, and Baseline score as 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. In the event that a rescue medication is used, a supplementary MMRM model will be applied on a dataset that excludes data collected after the initiation of the rescue medication. To assess the robustness of the MMRM analyses performed under the missing at random (MAR) assumption, and given the long half-life of LX9211, pattern mixture models (PMM) with copy reference-based multiple imputation methods will be applied to both datasets (with and without data collected after the initiation of the rescue medication). The imputed datasets will be combined by use of Rubin's rule and analyzed using an analysis of covariance (ANCOVA) model fitted for the fixed effects of treatment, the randomization factor of Baseline pain severity and the continuous fixed covariate of Baseline score. The number and percentage of patients who need rescue medication and/or prematurely dropout of the study will be summarized descriptively. For the continuous, secondary and other efficacy endpoints: ZBPI score, PGIC score, and NPSI score, measured at multiple time points, a similar modeling strategy used for the primary endpoint will be applied. The proportion of responders based on Question 5 of the ZBPI, the 11-point scale (0 [no pain] to 10 [pain as bad as you can imagine]) will be compared between treatments using a Cochran-Mantel-Haenszel test stratified by the randomization factor of Baseline pain severity. A non-responder imputation (NRI) rule will be applied for all analyses based on categorical variables to assign outcomes to missing observations. The qualitative patient interview substudy will be managed by a vendor (RTI-Health Solutions, Research Triangle Park, NC); data

	analysis methods will be detailed in a separate statistical analysis plan and will be reported separately.
PK/PD Assessments	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]
PK/PD Analysis	C_{p2hr} and C_{trough} values will be summarized by treatment group, at each time point, using descriptive statistics. [redacted]
Safety Assessments	Safety and tolerability of LX9211 will be assessed by collection and review of AEs, clinical laboratory results, ECG findings, and vital signs.
Safety Data Analysis	Safety analyses, based on the Safety Population, will involve examination of the descriptive statistics and individual patient listings for any effects of study treatment on clinical tolerability and safety. Summaries will be prepared by treatment group (ie, placebo and LX9211) and, by study visit where applicable. The incidence of AEs will be presented by severity and by relatedness as assessed by the Investigator. All safety data will be provided as listings. Treatment-emergent adverse event (TEAE) summaries will include the overall incidence of TEAEs, incidence of TEAEs (by System Organ Class [SOC] and Preferred Term [PT]), TEAEs by maximum intensity, TEAEs by relationship to study treatment, events leading to discontinuation of study drug, deaths, and SAEs. Vital signs, ECGs findings, PE findings, clinically significant PE findings, weight, and laboratory parameters (chemistry, hematology, and urinalysis) will be summarized descriptively at each time point. Actual and change from Baseline data will be calculated and summarized. In addition, shift table analyses will be presented for the laboratory data.

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2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	adverse event
AAK1	AP2 associated kinase 1
ADPS	average daily pain score
ALT	alanine aminotransaminase
ANOVA	analysis of variance
AP	alkaline phosphatase
AST	aspartate aminotransaminase
AUC	area under the curve
BLQ	below limit of quantification
BMI	body mass index
BUN	blood urea nitrogen
C_{p2hr}	2-hr plasma concentrations
C_{trough}	trough plasma concentrations
CBD	Cannabidiol
CCI	chronic constriction injury
CFR	Code of Federal Regulations
CI	confidence intervals
CMP	comprehensive metabolic panel
CNS	central nervous system
CRO	Contract Research Organization
DMC	data monitoring committee
eCRF	electronic Case Report Form
ECG	electrocardiogram
EMG	electromyogram
EOT	end of treatment
ERC	Ethics Review Committee

Abbreviation	Definition
eTMF	electronic trial master file
EW	early withdrawal
FDA	U.S. Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GMR	geometric mean ratio
HADS	Hospital Anxiety and Depression Scale
HbsAg	hepatitis B surface antigen
HCV Ab	hepatitis C virus core antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
LLOQ	lower limit of quantification
MAR	missing at random
MMRM	mixed-effects model repeated measures
MedDRA	Medical Dictionary for Regulatory Activities
NFR	nociceptive flexion reflex
NOAEL	no observable adverse effect level
NPSI	Neuropathic Pain Symptom Inventory
NRI	non-responder imputation
OTC	over-the-counter
PBMC	peripheral blood monocytes

Abbreviation	Definition
PD	pharmacodynamic
PE	physical examination
PGIC	Patient's Global Impression of Change
PK	pharmacokinetic(s)
PHN	postherpetic neuralgia
PRO	patient-reported outcome
RBC	red blood cells
SD	standard deviation
SAE	serious adverse even
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SSR	sample size reestimation
STZ	streptozotocin
TCA	tricyclic antidepressant
Tdap	tetanus, diphtheria and acellular pertussis vaccine, adult/adolescent formulation
UA	urinalysis
ULN	upper limit of the normal reference range
US	United States
VAS	visual analog scale
WBC	white blood cell
WHO-DD	World Health Organization Drug Dictionary
ZBPI	Zoster Brief Pain Inventory

3. Introduction

3.1 Background on LX9211 and Neuropathic Pain

Neuropathic pain is caused by a lesion or disease of the somatosensory nervous system such as herpes infection and diabetes, which can lead to chronic pain syndromes such as postherpetic neuralgia (PHN) and diabetic peripheral neuropathic pain (DPNP) (Costigan, 2009). As a consequence of these conditions, patients can experience hyperalgesia (increased pain from a normally painful stimulus), allodynia (pain elicited by a stimulus that does not normally evoke pain), and spontaneous pain (pain arising without an obvious triggering event). Despite the availability of approved drugs for the management of neuropathic pain, a significant unmet need remains. Specifically, these agents do not eliminate neuropathic pain for most patients with fewer than half achieving a 50% reduction in pain severity (Finnerup, 2010; Snedecor, 2014). In addition, undesirable side effects, such as dizziness, somnolence, weight gain, cognitive and motor impairment, are seen in patients treated with currently available analgesic therapies.

AP2 associated kinase 1 (AAK1) was first identified as a novel therapeutic target for neuropathic pain following testing of 3,097 homozygous mouse knockout lines in a broad, unbiased phenotypic screen (Kostich, 2016). AAK1 knockout mice showed markedly reduced persistent pain responses (Phase 2 flinching) in the formalin test but were otherwise normal in assays of acute pain (hotplate and formalin Phase 1 response) and motor function (Kostich, 2016). AAK1 knockout mice also failed to develop mechanical allodynia following ligation of the L4 and L5 spinal nerves (Chung model) confirming that AAK1 plays an important role in the development of persistent and neuropathic pain states (Kostich, 2016).

Given this desirable profile Lexicon initiated a discovery program to identify novel, small molecule, AAK1 inhibitors with suitable properties to progress into clinical development for the treatment of neuropathic pain.

LX9211 potently inhibits AAK1 with in vitro IC_{50} values ranging from 1.08 - 3 nM. In vivo studies show that acute oral administration of LX9211 reduced established thermal hyperalgesia in chronic constriction injury (CCI) rats and reduced established mechanical allodynia in streptozotocin (STZ)-treated rats. Separate studies confirmed that LX9211 engaged AAK1 in the rat spinal cord after oral administration. LX9211 showed low potential for motor impairment in rats with no effect observed on performance of the accelerating rotarod test. In the rat nociceptive flexion reflex (NFR) model, LX9211 increased the current threshold required to elicit an A-delta-related increase in the biceps femoris muscle electromyography (EMG) response after intravenous (IV) administration. Intravenous administration of LX9211 also reduced A-delta-related wind-up of the EMG response and plasma exposures achieved at doses

effective on NFR measures were within the same range as those required for efficacy in neuropathic pain models.

These results support the development of LX9211 for the treatment of neuropathic pain and link AAK1 inhibition to a major inhibitory pain pathway, which is a powerful modulator of spinal dorsal horn circuits required for neuropathic pain (Fairbanks, 2009).

3.2 LX9211 Nonclinical Pharmacology, Pharmacodynamics and Toxicology

Additional details can be found in the Investigator Brochure (IB).

3.2.1 In Vitro Pharmacodynamic Studies

LX9211 was evaluated in a series of in vitro studies to determine potency and selectivity for inhibition of human AAK1. LX9211 is a potent inhibitor of AAK1 with in vitro IC_{50} values ranging from 1.08 – 3 nM. LX9211 showed good selectivity for AAK1 in a kinase panel consisting of 268 different assays to measure inhibition of a broad range of kinase targets. LX9211 was also tested for additional pharmacological activity in a panel of 41 assays (39 targets) to assess modulation of enzymatic, ligand binding or functional activity at selected G-protein coupled receptors, monoamine transporters, ion channels, nuclear hormone receptors and enzymes. LX9211 showed modest potency for inhibition of radioligand binding to the norepinephrine transporter (IC_{50} = 0.275 µM, equivalent to 106 ng/mL of LX9211). The projected human maximum free plasma concentration (C_{max} values 16.6 ng/mL corrected for 92.3% protein binding) of LX9211 at the projected efficacious clinical dose is 1.28 ng/mL (ie, 16.6x [1-92.3%] = 1.28 ng/mL), indicating a margin of efficacy of approximately 83 at the IC_{50} concentration of norepinephrine inhibition.

3.2.2 In Vivo Pharmacodynamic Studies

In vivo studies conducted to support the development of LX9211 for the treatment of neuropathic pain include i) efficacy determinations in 3 neuropathic pain models in rats (CCI, STZ, and postherpetic neuralgia models), ii) demonstration of AAK1 target engagement in rat spinal cord, iii) investigation of the potential for motor impairment in the rat accelerating rotarod test, and iv) demonstration of efficacy in the rat NFR model, which is a translational model sensitive to a variety of established pain medications in humans (Sandrini, 2005). Results show that acute oral administration of LX9211 reduced established thermal hyperalgesia in CCI rats and reduced established mechanical allodynia in STZ-treated rats. The lowest dose achieving >50% inhibition was 0.3 mg/kg and 1 mg/kg, respectively and was associated with average plasma exposures of 18.7 nM and 92.3 nM, respectively, on completion of behavioral testing.

LX9211 showed potent in vivo efficacy in a rat model for post-herpetic neuralgia. Both single and multiple oral doses of 30 mg/kg LX9211 demonstrated almost complete inhibition of pain due to varicella-zoster virus (VZV) infection in this model. Separate studies confirmed that LX9211 engaged AAK1 in rat spinal cord after oral administration; the AAK1 binding site occupancy was 83.1% and 96% measured 3 hours (ie, at time to peak efficacy) after treatment with 0.3 and 1 mg/kg LX9211, respectively. LX9211 showed low potential for motor impairment in rats with no effect observed on performance of the accelerating rotarod test at oral doses up to 30 mg/kg (average plasma exposure 1.65 μM). In the rat NFR model LX9211 increased the current threshold required to elicit an A-delta related increase in the biceps femoris muscle electromyogram (EMG) response after intravenous (0.3 mg/kg) or intraperitoneal (0.1 or 1 mg/kg) administration. Intravenous administration of LX9211 (0.1 or 0.3 mg/kg) also reduced A-delta related wind-up of the EMG response and plasma exposures achieved at doses effective on nociceptive flexion reflex (NFR) measures were within the same range as those required for efficacy in neuropathic pain models.

3.2.3 Safety Pharmacology

A core battery of Good Laboratory Practice (GLP) compliant safety pharmacology studies were conducted to assess the effect of LX9211 phosphate on the central nervous system (CNS), respiratory system, and cardiovascular system using standard methodologies and procedures. In the CNS study in rats, transient mydriasis was observed at 8 hours postdose in rats administered 15 mg/kg and at 4- through 24-hours postdose in rats administered 60 mg/kg. No LX9211 phosphate related changes were present at 168 hours postdose. LX9211 phosphate produced no definitive, biologically relevant changes in assayed respiratory parameters (tidal volume, respiratory rate, minute volume) up to 168 hours postdose at doses up to 60 mg/kg in the rat.

LX9211 phosphate inhibited human ether-a-go-go related gene (hERG) current with an IC_{50} of 1.1 μM. No effects on the cardiovascular system in dogs were clearly attributed to the administration of LX9211 phosphate at doses up to 30 mg/kg. However, in the 30 mg/kg dose group, 3 out of 4 dogs had emesis within 10 minutes of dosing. In 1 dog that did not vomit following administration of 30 mg/kg (therefore, likely had higher exposure), the corrected QT (QTc) interval was slightly prolonged by up to 20 msec (+9%) at 3 hours postdose.

3.2.4 Summary of Pharmacology

LX9211 showed potent in vivo efficacy in nonclinical neuropathic pain models in the rat; the lowest oral dose that demonstrated >50% inhibition was 0.3 mg/kg and 1 mg/kg in the CCI and STZ models, respectively.

In safety pharmacology studies, LX9211 was found to have no definitive, biologically relevant effects on the respiratory systems in rats at 60 mg/kg (the highest dose tested in the study). In the CNS study in rats, LX9211 produced a transient mydriasis, which was most likely due to the known pharmacology of the compound and was not considered adverse. No effects on the cardiovascular system in dogs were clearly attributed to the administration of LX9211 phosphate at doses up to 30 mg/kg.

3.3 LX9211 Toxicology

GLP-compliant toxicology studies with LX9211 phosphate of 4- and 13-weeks duration have been conducted in the rat and the dog. The no observed adverse effect level (NOAEL) for LX9211 phosphate was determined to be 10 mg/kg/day after 13 weeks of dosing in the rat and 5 mg/kg/day after 13 weeks of dosing in the dog. LX9211 phosphate tested negative in the standard battery of in vitro and in vivo genetic toxicology studies.

The effects of LX9211 on embryo-fetal development have been assessed in the rat and the rabbit. In the rat, the NOAEL was determined to be 10 mg/kg/day. In the rabbit, the NOAEL was 4 mg/kg/day

Additional details can be found in the IB.

3.3.1 Preclinical GLP-Compliant Toxicology Studies in Rats

In the 4-week study, LX9211 phosphate was administered by oral gavage to male and female rats at dose levels of 0, 3, 15, or 60 mg/kg/day. LX9211-related findings were non-adverse, generally reversible, and included infrequent clinical observations of decreased body weight and food consumption; minor clinical pathology effects; and vacuolation of macrophages in the lungs and epithelial cells in bile ducts, the main pancreatic duct, uterine glands, and epididymis that were consistent with phospholipidosis. Decreased body weight was associated with a decrease in the weight of prostate and atrophy (minimal) and decreased weight and secretions of seminal vesicles in male rats at 60 mg/kg/day. Assay results confirm that LX9211 is non-genotoxic. Based on the results of this study, the NOAEL for LX9211, administered as LX9211 phosphate by oral gavage for 4 weeks to rats, is 60 mg/kg/day. This corresponds to a Week 4 C_{max} of 3010 and 4420 ng/mL for males and females, respectively (mean of 3,630 ng/mL), and corresponding AUC_{0-24} of 65,000 and 94,900 ng*hr/mL, respectively (mean 79,200 ng*hr/mL).

In the 13-week rat study, LX9211 phosphate was administered by oral gavage to male and female rats at dose levels of 0, 3, 10, or 60 mg/kg/day. At the high dose (60 mg/kg/day), there were 3 unexplained deaths (2 on Day 11 and 1 on Day 69). In addition, 5 high-dose animals experienced a total of 6 short (<1 minute) clonic convulsions; most occurred during the last 3

weeks of dosing. No convulsions or deaths occurred at any of the lower doses. LX9211 phosphate-related, non-adverse effects included minor clinical observation and clinical pathology findings in animals administered 60 mg/kg/day. Adverse decreased body weight changes were noted for animals administered 60 mg/kg/day. Non-adverse cytoplasmic vacuolation, consistent with phospholipidosis, was observed in the kidney, lung, thyroid, pancreas, liver, epididymis, and uterus of animals administered 60 mg/kg/day and in the lung, uterus, liver, pancreas, and epididymis of animals administered 10 mg/kg/day. Adverse microscopic findings were noted in the kidneys of animals administered 60 mg/kg/day, characterized by slight to moderate chronic progressive nephropathy associated with increased kidney weights. Slight atrophy of the prostate was noted at 60 mg/kg/day. Based on the results of this study, the NOAEL for LX9211, administered as LX9211 phosphate by oral gavage for 13 weeks to rats, is 10 mg/kg/day. This corresponds to a Week 13 C_{max} of 922 and 1,370 ng/mL for males and females, respectively (mean of 1,090 ng/mL), and corresponding AUC_{0-24} of 15,200 and 23,100 ng*hr/mL, respectively (mean 19,100 ng*hr/mL). This exposure at the NOAEL is approximately 10-fold higher than that projected at the dose in the current PHN study.

3.3.2 Preclinical GLP-Compliant Toxicology Studies in Dogs

In the 4-week study, LX9211 phosphate was administered by oral gavage to male and female beagle dogs at dose levels of 0, 1, 2.5, or 5 mg/kg/day. LX9211-related pathology findings included minimal to mild increases in white blood cell (WBC) and absolute neutrophil counts and decreases in absolute lymphocyte and eosinophil counts in some animals at ≥1 mg/kg/day that were considered stress related. Minimal acute inflammation in the urinary bladder was noted in 3/6 (2 males and 1 female) animals, with slight urothelial hyperplasia in 2 of these animals, and minimal focal ulcer in the urinary bladder in 1 of these animals administered 5 mg/kg/day. Minimal aortic mineralization was observed in 1 female animal in the low-dose group and 1 female animal in the mid-dose group. Minimal to slight aortic mineralization was observed in 2 female animals in the high-dose group. Based on the results of this study, the NOAEL for LX9211 phosphate, administered by oral gavage for 4 weeks to dogs, is 2.5 mg/kg/day. This corresponds to a Week 4 C_{max} of 133 and 125 ng/mL for males and females, respectively (mean 129 ng/mL), and corresponding AUC_{0-24} of 1,860 and 1,090 ng*hr/mL, respectively (mean 1,470 ng*hr/mL).

LX9211 phosphate was also administered by oral gavage for 13 weeks to male and female beagle dogs at a dose of 1, 2.5, or 5 mg/kg/day. No LX9211 phosphate-related clinical observations, ophthalmic findings, physical examination findings, or differences in body weight, body weight change, food consumption, heart rate, body temperature, or pulse oximetry occurred. No ECG changes were attributed to LX9211 phosphate, and no LX9211 phosphate-

related changes in hematology or urinalysis (UA) test results were noted. Two minor LX9211 phosphate-related clinical pathology findings observed on Day 92 of the dosing phase in male beagles that received 5 mg/kg/day were minimally increased fibrinogen and globulin concentrations; these findings suggested an inflammatory response and lacked microscopic correlates, exhibited evidence of reversibility, and were considered not adverse based on their small magnitude. At the terminal sacrifice, 1 male receiving 2.5 mg/kg/day LX9211 had minimal muscle degeneration in the urinary bladder. At recovery sacrifice, 1 male receiving 5 mg/kg/day also had the same finding. The severity in both cases was minimal. This finding occurs as a background finding in beagle dogs (Cain, 2000).The urinary bladder changes occurred at a low incidence and severity, similar to published data indicating no associated clinical signs or evidence of bladder dysfunction. The UA data from these animals was unremarkable. The relationship of the urinary bladder changes to treatment, if any, is not clear. Based on the results of this study, the NOAEL for LX9211 phosphate, administered by oral gavage for 13 weeks to dogs, is 5 mg/kg/day. This dose level corresponded to mean C_{max} of 506 and 515 ng/mL for males and females, respectively (mean 511 ng/mL), and corresponding AUC0-24 of 6,440 and 6,810 ng*hr/mL for males and females, respectively (6,620 ng*hr/mL).

3.3.3 Embryo-Fetal Development Study in the Rat

The effects of LX9211 phosphate on embryo-fetal development has been assessed in the rat. Doses evaluated were 0, 1, 3, and 10 mg/kg/day. Test article-related non-adverse effects included decreased mean body weight and body weight gain (1, 3, and 10 mg/kg/day), decreased food consumption (3 and 10 mg/kg/day), reduced adjusted fetal weight parameters (10 mg/kg/day), and unossified phalanx hindlimb skeletal variations (10 mg/kg/day). No test article-related effects on maternal clinical or macroscopic observations, reproductive performance, or fetal external, visceral or skeletal malformations were noted. Based on the results of this study, the NOAEL for LX9211, administered as LX9211 phosphate by oral gavage to pregnant rats during the period of organogenesis, is 10 mg/kg/day. On Gestation Day 12 for this dose level, the C_{max} and AUC0-24 were 882 ng/mL and 12,000 ng*hr/mL, respectively, for LX9211.

3.3.4 Embryo-Fetal Development Study in the Rabbit

In the rabbit, doses of LX9211 phosphate evaluated were 0, 0.6, 2, and 4 mg/kg/day. No test article related effects were noted on maternal body weight, food consumption, clinical or macroscopic observations, reproductive performance, cesarean section parameters, embryofetal toxicity, or fetal development. Based on the results of this study, the NOAEL for LX9211, administered as LX9211 phosphate by oral gavage to pregnant rabbits during the period of

organogenesis, is 4 mg/kg/day. On Gestation Day 13 for this dose level, the C_{max} and AUC_{0-24} were 261 ng/mL and 4200 ng*hr/mL, respectively, for LX9211.

3.4 Clinical Trials of LX9211 in Humans

Three clinical studies have recently completed: LX9211.1-101-NRM, A Phase 1, Randomized, Double-blind, Placebo-controlled Ascending, Single-dose Study to Determine the Safety and Tolerability of Orally Administered LX9211 in Healthy Human Participants (SAD); LX9211.1-102-NRM, A Phase 1, Randomized, Double-blind, Placebo-controlled Ascending Multiple-dose Study to Determine the Safety and Tolerability and Pharmacokinetics of Orally Administered LX9211 in Healthy Volunteers (MAD); and LX9211.1-103-NRM, A Phase 1, Open-label, Nonrandomized, 2-part Study to Evaluate the Absorption, Metabolism, Excretion, Mass Balance, and Absolute Bioavailability of ^{14}C-LX9211, Following Oral and Intravenous Administration in Healthy Male Subjects.

The SAD and MAD studies included females of nonchildbearing potential and males between the ages of 18 to 65 years. A total of 146 subjects were enrolled in the 2 studies, 112 of whom were randomly assigned to receive LX9211.

The results from the SAD study showed that LX9211 was generally well tolerated in healthy normal subjects at single doses up to 300 mg. Results from cohorts exposed to single-dose LX9211 up to 300 mg are summarized as follows:

Adverse events were mild to moderate in intensity; there were no severe AEs, deaths, SAEs, or withdrawals due to AEs. The most common AEs were dizziness and headache. One subject in the 300 mg single-dose cohort experienced orthostatic tachycardia with an onset at 1-hour postdose and which lasted for 8 days. This event was reported by the Investigator as mild in intensity and related to study drug.

Systemic exposure to LX9211 (C_{max}, AUC_{0-24}, AUC_{0-96}, and AUC_{0-inf}) increased from 5 to 300 mg in an apparent dose-proportional manner when examined as the log functions of dose and exposure. Median T_{max} of LX9211 was approximately 8-12 hours postdose and the mean $t_{1/2}$ ranged from 143 to 197 hours (6 to 8 days).

Based on the pharmacokinetic (PK) profile of LX9211 in the SAD study, subjects in the MAD study were given a loading dose on Day 1, followed by a daily maintenance dose on Days 2-14. This dosage regimen permitted steady state to be achieved quickly and then maintained for the duration of the study. Results from this study showed that LX9211 was well tolerated in healthy normal subjects receiving multiple doses (14 days) up to 200 mg loading dose. All AEs were mild in intensity; there were no severe AEs, deaths, or SAEs. One patient discontinued due to reported AEs: allergic rash, urticaria, and angioedema. All AEs were assessed as mild and

resolved within a few days after being treated with a single oral dose of diphenhydramine. Overall, the AEs observed in the MAD study were similar to those reported in the SAD study. In both studies, the most common AEs were headache and dizziness in patients treated with LX9211, with the events occurring at higher frequency at doses at or above 100 mg. With few exceptions, these events occurred 1-3 days after dosing, lasted for 1-2 days, were considered mild in intensity, and resolved spontaneously. No clinically significant comprehensive metabolic panel (CMP), UA findings, or bladder dysfunction-related AEs were reported in any subject treated with LX9211 in the SAD or MAD studies with LX9211.

In study LX9211-103, a cohort of 6 male subjects was exposed to a single oral dose of 14C-LX9211 (nominal 50 mg free drug, approximately 52uCi). Drug-related material in urine and feces was collected for up to 34 days. The mean total recovery of administered radioactivity was 77.9%, with 48.7% recovered in urine and 29.2% recovered in feces. There were no serious adverse events (SAEs) and the adverse events (AEs) experienced, were similar to those seen in the SAD and MAD studies; all were mild in severity. In the same study, a separate cohort of 6 subjects underwent an evaluation to establish the absolute oral bioavailability of LX9211. A single oral dose of 50 mg of LX9211 was administered, followed by an intravenous microdose infusion of 14C-9211 (50 μg/200nCi). The mean oral bioavailability of LX9211 was 89.4%. Again, there were no SAEs and the AEs experienced were similar to those seen in the SAD and MAD studies; all were mild in severity.

3.5 Rationale for Current Study

3.5.1 Rationale for Selection of Dose

The loading and maintenance dose level of LX9211 selected for evaluation in the current study was chosen based upon the safety, tolerability, and PK data observed from the prior single-dose and multiple-dose Phase 1 studies.

The doses studied in the SAD and MAD studies, in healthy volunteers, ranged from 5 to 300 mg. Single-dose administration demonstrated linear PK up to the highest tested dose (300 mg). There were no deaths, SAEs, discontinuations due to an AE, AEs of severe intensity, or any clinically significant laboratory, vital sign, physical exam (PE), or electrocardiogram (ECG) findings.

Multiple-dose administration demonstrated linear PK up to the highest tested dose (200 mg). There were no deaths, SAEs, discontinuations due to an AE, AEs of severe intensity, or any clinically significant laboratory, vital sign, PE, or ECG findings.

Based on the observed safety and tolerability data from single doses up to 300 mg and multiple doses up to 200 mg for 14 days, the dose level selected in this study, 200 mg loading dose

followed by 20 mg maintenance doses, respectively, are expected to be well tolerated and represent an adequate range for dose exploration.

3.6 Rationale for Study Design and Control Groups

The randomized, placebo-controlled, double-blind clinical design allows for unbiased comparison of efficacy and safety between LX9211 and placebo. The treatment duration (6 weeks) selected for this study was chosen based on the expectation of seeing an efficacy signal for the LX9211 200 mg treatment, which was based on human safety and tolerability.

Use of a concurrent placebo control, randomization, and double-blind administration of study drug are intended to minimize bias. Implementation of an unblinded interim analysis will allow for a reestimated increase in the sample size if indicated by the interim results. The study is designed as a group sequential trial to accommodate the interim analysis, and to improve upon such a design, the interim analysis effect size result is used not only to possibly increase the sample size, but to aid in decisions of early stopping for futility. The option of sample size reestimation (SSR) allows the study to power for a more optimistic effect, thereby minimizing up-front costs, while assuring a good probability of detecting a smaller important effect size by increasing the sample size if required.

4. Study Objectives

4.1 Primary Objective

To evaluate the efficacy of LX9211 in reducing pain related to postherpetic neuralgia (PHN)

4.2 Secondary Objective

To assess other effects and patient reported outcomes of LX9211 versus placebo during and following the Week 6 double-blind Treatment Period

4.3 Other Objectives

- Change from Baseline to Week 6 in the Neuropathic Pain Symptom Inventory (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 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

5. Investigational Plan

5.1 Overall Study Design

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in patients with PHN.

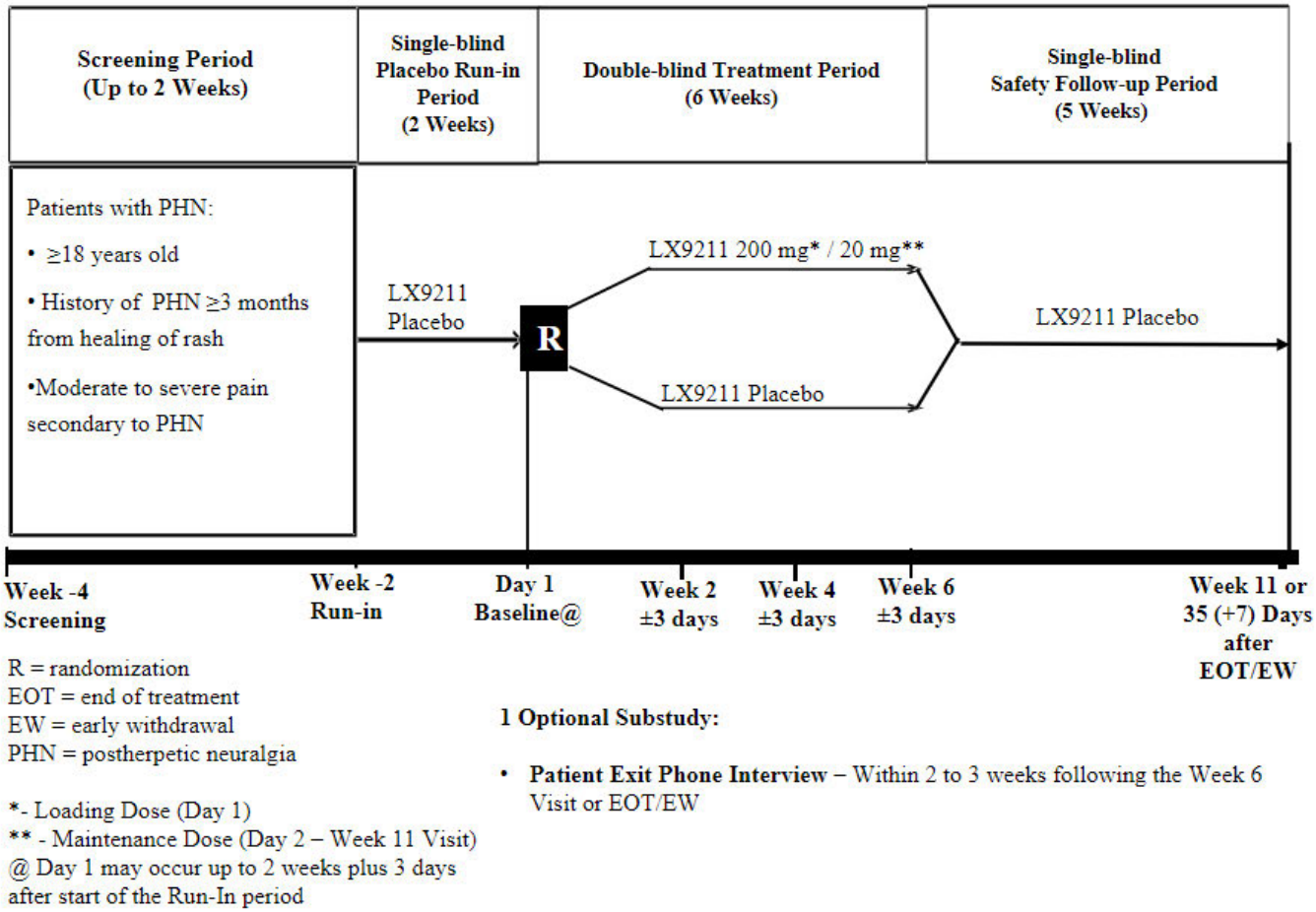
Scheduled study visits in the clinic will occur during Screening; at the initiation of the 2-week single-blind placebo Run-in Period; on Day 1 (Baseline), and during Weeks 2, 4, and 6 of the double-blind Treatment Period, and Week 11 of the single-blind Safety Follow-up Period.

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

Eligible patients may continue use 1 medication prescribed for PHN including pregabalin, gabapentin, and tricyclic antidepressant (TCA) 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 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 (OTC), 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.

The treatment schema is summarized in Figure 5.1-1.

Figure 5.1–1 Treatment Schema



R = randomization
EOT = end of treatment
EW = early withdrawal
PHN = postherpetic neuralgia

*- Loading Dose (Day 1)
** - Maintenance Dose (Day 2 – Week 11 Visit)
@ Day 1 may occur up to 2 weeks plus 3 days after start of the Run-In period

1 Optional Substudy:

- **Patient Exit Phone Interview** – Within 2 to 3 weeks following the Week 6 Visit or EOT/EW

5.1.1 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 of 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:

5.1.2 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 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 have completed ≥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.

5.1.3 Randomization/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, once daily 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 hr 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 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 and at each clinic visit thereafter, patients will be provided individual bottles of study drug. Sufficient quantity of study drug will be provided to allow prescribed daily dosing until the next scheduled clinic visit. Each bottle will be labeled with a 1-panel, double-blind label printed in black. Prior to dispensation, the Investigator/qualified designee will complete spaces on the study drug label to specify the Patient Number, Date Dispensed, and Investigator Name. In addition, the protocol number, batch number, quantity of tablets, route of administration, directions for use, bottle number, and storage conditions will be indicated.

Except on days of clinic visits, patients should be instructed to dose with double-blind study drug at approximately the same time each day and before the first meal of the day. One tablet of double-blind study drug should be taken with 8 ounces of water and should be taken whole. If a patient misses a dose by more than 12 hours, that dose should be skipped, and the next dose should be taken as scheduled. No double doses should be taken, and dose reductions are not permitted.

On days of clinic visits, double-blind study drug will not be taken in the morning prior to the scheduled clinic visit. Patients will take their assigned dose of double-blind study drug for that day per instructions from clinic staff, based on scheduled procedures. The date and time of administration of the last dose of study drug prior to the clinic visit will be recorded in the eCRF.

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]

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 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.

5.1.4 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 ZBPI, record the use of rescue medication (acetaminophen), and rate the interference with sleep using the ZBPI.

5.1.5 Optional Substudy

During the Screening Visit, patients may choose to participate in an optional substudy.

The optional substudy, a qualitative patient interview, will include approximately 30 patients. The telephone interview will be designed to gain insight and understanding of patients' experiences with symptoms of PHN and to assess relevance and clinical meaningfulness of symptom improvements (eg, reduction in pain) with LX9211 treatment.

6. Study Population

Male or female patients 18 years or older will be enrolled. Patients will have a diagnosis of postherpetic neuralgia defined as pain in the dermatomal distribution of an acute herpes zoster

skin rash, persisting for ≥3 months from the healing of herpes zoster skin rash. Patients will have to meet pain criteria at the end of the Run-in Period.

The proposed sample size is 74 patients, 37 patients per treatment group. This estimate takes into account an expected uniform dropout rate of 15%. The sample size may be increased to a maximum of 148 patients based on a planned interim analysis that allows for conduct of a sample size reestimation procedure.

The substudy will enroll approximately 30 patients to participate in a qualitative patient interview.

6.1 Inclusion Criteria

Patients must meet **all** of the following criteria to be considered eligible to participate in the study. For patients not meeting eligibility requirements, the reason for exclusion must be recorded. **Note**: Patients who are not eligible because of laboratory result(s) may have the laboratory test(s) repeated **once** during the Screening Period, at the discretion of the Investigator, to determine eligibility:

1. Patient has given written informed consent to participate in the study in accordance with local regulations
2. Adult male or female patients ≥18 years of age at the Screening Visit:
    a. Females of childbearing potential must have a negative serum or urine pregnancy test prior to the start of study drug. In the case of positive urine pregnancy testing, a negative serum sample for pregnancy testing, to confirm that the patient is not pregnant, must be obtained prior to start of study. They must also agree to use adequate methods of contraception which include the following: condom with spermicidal gel, diaphragm with spermicidal gel, coil (intrauterine device), surgical sterilization, vasectomy, oral contraceptive pill, depo-progesterone injections, progesterone implant (ie, Implanon®), NuvaRing®, Ortho Evra®
    b. Nonsterile male patients with sexual partners of childbearing potential must agree to use adequate methods of contraception from Baseline through the Week 11 Visit
3. Presence of PHN pain that is present for ≥3 months after healing of herpes zoster skin rash affecting a single dermatome (Patients with more than 1 involved dermatome may also be included, provided the affected dermatomes are contiguous)
4. Moderate to severe pain as confirmed by average pain score using scores recorded in the pain diary in the 14 days prior to randomization (Run-in Period)

5. At least 80% compliance with dosing during the 2-week Run-in Period, and 70% compliance with completion of the daily diary during the second week of the Run-in Period
6. Willing to adhere to the prohibitions and restrictions specified in the protocol

6.2 Exclusion Criteria

Patients who meet **any** of the following criteria will be excluded from participating in the study:

1. Presence of other painful conditions that may confound assessment or self-evaluation of PHN:
    a. Patient should not have any other neurological disorder or conditions that can cause symptoms that may mimic peripheral neuropathy or that might confound assessment of PHN pain.
    b. Other causes of diffuse painful peripheral neuropathy such as: paraproteinemia, untreated hypothyroidism (previously treated hypothyroidism not excluded if treated and euthyroid for ≥6 months), vitamin B12 deficiency, neurologically-evident vasculitis, malignancy, amyloidosis, renal insufficiency, connective tissue disease (eg, Sjogren's, systemic lupus erythematosus), porphyria, complex regional pain syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, alcoholism, HIV, hepatitis, uremia, syphilis, myeloma, or other systemic disease associated with a secondary painful neuropathy should be excluded.
    c. Patient should not have had any exposure to drugs/toxic environmental agents known to cause neuropathy.
2. Over the past year, met Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria (American Psychiatric Association, 2016) for a major depressive episode, any active, significant psychiatric disorders (eg, neurocognitive disorder, anxiety disorder, psychosis, bipolar disorder), or a history of clinically significant drug or alcohol use disorder that would, in the Investigator's opinion, interfere with the assessment and evaluation of pain during the study
3. Mood and anxiety disorder scores defined by Hospital Anxiety and Depression Scale (HADS) ≥13
4. Suspected or likely diagnosis of trigeminal neuralgia
5. Use of opioid medications for management of PHN within the 2 months prior to the Screening Visit. **Note:** Brief use (<1 week) of opioid medication for management of

non-PHN acute pain (eg, tooth extraction/acute injury) ≥2 months prior to Screening Visit is permitted.

6. Use of NSAIDs for the specific treatment of PHN pain
7. Use of more than 1 permitted concomitant medications for the treatment of PHN. **Note:** Patients may washout additional PHN medications ≥1 month prior to the Screening Visit to reach the 1 permitted medication.
8. For non-opioid medications patient uses and is unwilling/unable to discontinue use of prohibited medications and therapies, (eg, benzodiazepines, dextromethorphan, herbal medications, mexiletine HCl, adenosine, topical analgesics including lidocaine and capsaicin), applied to the same area of the body affected by PHN pain, nerve blocks, acupuncture, or other medications indicated for neuropathic pain. A patient using any of these interventions for neuropathic pain must discontinue the medication ≥1 month prior to starting the Screening Period and for the duration of the study. **Note:** This exclusion criterion does not include analgesics that are not specifically prescribed for treatment of neuropathic pain (eg, nonsteroidal anti-inflammatory drugs [NSAIDs], aspirin, acetaminophen). In addition, patients who are prescribed antidepressants for a mental health disorder are eligible to participate as long as they do not meet Exclusion Criteria 2-3.
9. A positive urine drug test for drugs of abuse including cannabinoids. **Note:** Cannabidiol (CBD), if used for mood or sleep, is acceptable. If used for PHN it would be allowed if it is the only concomitant medication being taken for PHN. If not, the only medication being taken for PHN, it should be withdrawn ≥1 month prior to Screening.
10. Patient has hepatic impairment at Screening, defined as any of the following: aspartate aminotransferase (AST) >2X upper limit of the normal reference range (ULN), alanine aminotransferase (ALT) >2X ULN, serum total bilirubin (TB) >2X ULN. **Note**: If it is the opinion of the Investigator and the Medical Monitor that an increase in bilirubin is due to Gilbert's syndrome, then the patient may participate.
11. Patient has abnormal kidney function test (estimated glomerular filtration rate [eGFR] <60 mL/min as calculated using the Cockcroft-Gault equation) at Screening or renal dysfunction requiring hemodialysis
12. Patient has any of the following medical conditions or disorders: epilepsy or seizure disorder requiring treatment with antiepileptic drugs
13. Presence of clinically significant physical examination (PE) findings other than PHN, or laboratory or ECG findings that in the opinion of the Investigator, Medical Monitor,

and/or the Sponsor, may interfere with any aspect of study conduct or interpretation of results including:

a. any clinically significant abnormal heart rate or rhythm
b. other ECG abnormalities that are clinically relevant
c. BP >160/100 mm Hg or <90/50 mm Hg
d. presence of risk factors for torsade de points (eg, family history of long QT syndrome; personal history of NYHA class III/IV heart failure or structural heart disease)

14. Receipt of any investigational agent within 30 days or 5 half-lives, whichever is longer, prior to Baseline/Randomization on Day 1
15. Receipt of any therapeutic protein, antibody/biologic- or antibody-based agents (eg, growth hormones or monoclonal antibodies) within 3 months prior to dosing on planned Day 1. **Note:** Preventative vaccines (eg, influenza, pneumococcal, Tdap), will be allowed if administered >7 days prior to dosing. Patients who have previously received the shingles vaccine, but subsequently develop PHN and meet all inclusion and exclusion criteria, are eligible to participate.
16. Prior exposure to LX9211
17. History of any serious adverse reaction or hypersensitivity to any inactive component of study drug, unless the reaction is deemed irrelevant to the study by the Investigator, Medical Monitor, and/or the Sponsor
18. Presence of any skin condition, such as ulcers, which could interfere with assessment of PHN
19. Existence of any postsurgical or medical condition that, in the judgment of the Investigator, Medical Monitor, and/or the Sponsor, might interfere with the absorption, distribution, metabolism, or excretion of LX9211, including bariatric surgery, cholecystectomy, or any other GI surgery, except appendectomy and hernia repair, which are acceptable
20. History of any major surgery within 3 months prior to Baseline or surgery that is anticipated to be performed during the study period
21. History of any active infection within 30 days prior to Baseline, if deemed clinically significant by the Investigator, Medical Monitor, and/or the Sponsor
22. Malignancy or active treatment for malignancy (ie, radiation or chemotherapy, including monoclonal antibodies) within 5 years prior to the Screening Visit. **Note:** Patients with squamous or basal cell carcinomas of the skin, carcinomas in situ of the cervix or uterus, ductal breast cancer in situ, resected low-grade prostate cancer, or other malignancies

that, in the opinion of the Investigator and the Medical Monitor are considered cured, may participate.

23. Donation or loss of >500 mL of blood or blood product within 3 months prior to Baseline
24. Inability or difficulty swallowing whole tablets
25. Any other condition that compromises the ability of the patient to provide informed consent or to comply with the objectives and procedures of this protocol, as judged by the Investigator, Medical Monitor, and/or the Sponsor
26. Unable or unwilling to adhere to the requirements of the protocol, or communicate or cooperate with the Investigator and/or their staff for any reason
27. Patient refuses to participate in processes if established by the Sponsor, to minimize duplicate patients (Verified Clinical Trials)
28. Employees, or relatives of the Sponsor, Investigator or study center staff, with direct involvement in the proposed study or other studies under the discretion of the Investigator or study center
29. Patients is immunocompromised (eg, secondary to transplant or require active immunosuppressive drugs)

6.3 Criteria for Stopping Treatment/Study Withdrawal

A patient may also be discontinued from the study for the following medical or administrative reasons:

- Withdrawal of consent by the patient or legal guardian
- Noncompliance, including refusal of the study drug and/or failure to adhere to the study requirements as in the study protocol
- Investigator decides that, in the interest of the patient, it is not medically acceptable to continue participation in the study
- The Sponsor terminates the study

Note: If a patient is discontinued from study drug before completing the entire duration of the Treatment Period up through Week 6/EOT/EW, they should be encouraged to complete all end-of-study assessments and to agree to report any AEs, including SAEs (see Section 9.4) for 35 days following their last dose of study treatment. The date the patient is discontinued and the primary reason for study drug discontinuation and termination of participation must be recorded on the eCRF.

6.3.1 Lost to Follow-up

If a patient does not return to the clinic, attempts should be made to contact the patient (or a previously approved designee such as a caregiver, partner, or family member) to determine the reason for discontinuation. At minimum, 3 documented attempts, including 1 via certified mail, should be made to contact the patient before considering the patient lost to follow-up.

6.4 Criteria for Termination of the Study or of a Site's Participation

If the Sponsor, Investigator, study monitor, or regulatory officials discover conditions arising during the study that indicate that the study should be halted or that the study center's participation in the study should be terminated, this action may be taken after appropriate consultation between the Sponsor and Investigator. Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the patients enrolled in the study
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product
- Failure of the Investigator to enroll patients into the study at an acceptable rate
- Failure of the Investigator to comply with pertinent Food and Drug Administration (FDA) regulations
- Submission of knowingly false information from the research facility to the Sponsor, study monitor, or the FDA
- Insufficient adherence to protocol requirements
- Results from a planned interim analysis; see Section 6.4.1 for details

Study termination and follow-up would be performed in compliance with the conditions set forth in the following sections of the Code of Federal Regulations: 21 CFR 312.50 and 21 CFR 312.56.

6.4.1 Termination of the Study Based on Planned Interim Analysis

The study may be terminated based on the conduct of a formal interim analysis of futility. The interim analysis will be performed when the first 38 patients have been accrued and followed to endpoint at Week 6 or dropped out from the trial earlier, whichever event occurs first. Enrollment will not be temporarily halted while data for the interim analysis is being reviewed. The sample size may be increased based on the interim analysis Details of

the futility analysis are given in Section 10.4.5.7 of this protocol, and in the Statistical Analysis Plan (SAP) and Data Monitoring Committee (DMC) Charter documents.

In addition to the planned interim analysis for futility, 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 as follows: 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 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.

6.5 Clinical Stopping Rules

Not applicable; however, criteria for individual patient withdrawal or study termination are summarized in Section 6.3 and Section 6.4, respectively.

6.6 Method of Assigning Patients to Treatment

Patients will be randomly assigned between 2 parallel treatment groups in a 1:1 manner. A randomization Schedule will be centralized and stratified by moderate or severe pain as derived from the ADPS collected during the Run-in period. The desired balances will be accomplished by use of randomly permuted blocks of fixed size. An Interactive Voice/Web Response System (IXRS) will be used as a central mechanism to assign patients to study treatment.

6.7 Blinding and Unblinding of Study Drug

In this double-blind study, the designated group and treatment assigned to each patient will not be revealed to the Investigator, the patient, or the Sponsor or their designee, until the decision is made to unblind the study. Data from individual patients may be unblinded if deemed medically necessary by the Investigator in consultation with the Sponsor, or as required by regulation for reporting purpose in the case of an unexpected and related SAE. The IXRS will be used to perform emergency unblinding by authorized individuals.

The randomization schedule will be maintained by the designee performing IXRS for this study. Investigators, study site personnel associated with this trial, patients, and the Sponsor and its designees involved in the conduct of the study will remain blinded to individual patients' treatment assignments until database lock.

During the study, the blind is to be broken only when the safety of a patient is at risk and the treatment plan is dependent on the study treatment received. If the unblinding occurs without the knowledge of the Sponsor and/or designee, the Investigator must notify the Sponsor and/or designee as soon as possible and no later than 24 hours from the unblinding. All circumstances surrounding a premature unblinding must be clearly documented in the source records.

The Sponsor's designee performing IXRS will not release the randomization schedule to any party except upon formal written request by the Sponsor at study end. The request must be approved by the appropriate Sponsor personnel, according to the Sponsor's standard operating procedures (SOPs). Details of any disclosure of the randomization schedule will be recorded in the site's study files and the electronic Trial Master File (eTMF). A copy of the randomization schedule will also be sent to the Sponsor and/or designee. The blinding of the study will be broken after the database has been locked. To maintain continuous blinding and study integrity, analysis will be conducted by an independent statistician, and measures will be taken to ensure the validity of the data.

6.8 Replacement of Patients

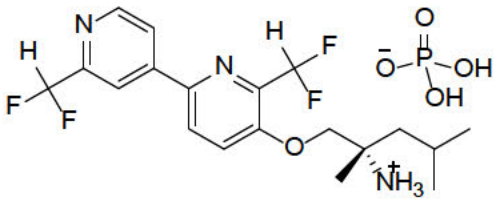
Patients will not be replaced in this study.

7. Treatment

7.1 LX9211

7.1.1 Identity

LX9211 phosphate is a white to off white to yellow solid with a melting point of approximately 184°C. The solubility of LX9211 phosphate in water is 26.8 mg/mL at 25°C. The molecular formula is $C_{19}H_{23}F_4N_3O \bullet H_3PO_4$, the formula weight is 483.40, and the chemical structure is:



The molecular weight of the free base is 385.41.

Physical characteristics, solubility, drug substance manufacture, and stability testing are being performed in compliance with current Good Manufacturing Practice (GMP) at Wuxi Apptec (Shanghai, China).

7.1.2 Tablets

The study drug dose form consists of white to off-white round coated tablets containing 20 mg, or 50 mg of LX9211. All the tablets are visually similar in color, size, and shape.

Tablet inactive ingredients include silicified microcrystalline cellulose, dibasic calcium phosphate anhydrous, croscarmellose sodium, talc, colloidal silicon dioxide, and hydrogenated vegetable oil.

7.1.3 Packaging, Labeling, and Storage

LX9211 50-mg tablets are packaged in 30 cc high density polyethylene (HDPE) bottles containing pharmaceutical coil and a child resistant polyethylene screw cap with induction seal. Each bottle contains 2 tablets.

LX9211 20-mg tablets are packaged in 30 cc HDPE bottles containing pharmaceutical coil and a child resistant polyethylene screw cap with induction seal. Each bottle contains 20 tablets.

LX9211 tablets in HDPE bottles should be stored at 25°C (77°F); excursions are permitted 15°C to 30°C (59°F to 86°F). Stability testing of all the tablet strengths of LX9211 (50-mg and 20-mg) is ongoing.

7.1.4 Placebo

The placebo dose form is visually similar in color, size, and shape to LX9211 tablets.

Tablet ingredients include silicified microcrystalline cellulose, dibasic calcium phosphate anhydrous, croscarmellose sodium, talc, colloidal silicon dioxide, and hydrogenated vegetable oil.

Placebo tablets are packaged in 30 cc HDPE bottles containing pharmaceutical coil and a child resistant polyethylene screw cap with induction seal. The 50-mg bottle contains 2 placebo tablets while the 20-mg bottle contains 20 placebo tablets.

Placebo tablets in HDPE bottles should be stored at 25°C (77°F); excursions are permitted 15°C to 30°C (59°F to 86°F). Stability testing of placebo tablets is ongoing.

7.2 Prior and Concomitant Medications

7.2.1 Prior Medication

All medications (prescription and OTC) taken within 30 days prior to Screening will be recorded on the eCRF as a prior medication.

7.2.2 Concomitant Medication

All medications and other treatments ongoing or taken from the start of the Screening Period, through the end of the Safety Follow-up Period of the study will be recorded on the eCRF as concomitant medication. This includes any ongoing medications for the treatment patients' PHN (ie, gabapentin, pregabalin, and tricyclic antidepressant medications).

7.3 Prohibited Medication

Use of any new medications prescribed or OTC for treatment of PHN pain is not permitted during the course of the study. Only the acetaminophen provided by the Sponsor as a rescue medicine may be used during the course of the study. The use of personally acquired acetaminophen is prohibited. Use of any opioid medication for the management of PHN within the 2 months prior to Screening is not permitted. **Note:** Brief use (<1 week) of opioid medication for management of non-PHN acute pain (eg, tooth extraction/acute injury) ≥2 months prior to Screening Visit is permitted.

All medications, including the study drug, taken by patients during the study will be captured in the source documents and recorded on the eCRF.

7.4 Administration of Study Drug

LX9211 (50-mg and 20-mg) will be supplied in tablet form to be taken orally. A placebo, that is visually similar in appearance to the LX9211 tablets, will be taken by patients assigned to the placebo group.

On Day 1 of the Run-in Period, at the clinic, patients will be given 4 tablets from their bottle of Run-in study drug and will swallow it with 8 ounces (240 mL) of room temperature water. Each patient’s hands and mouth will be checked to ensure they have swallowed the tablets. On Days 2 through 14, patients will be instructed to take their daily dose of study drug before the first meal of the day with 8 ounces of room temperature water. If a patient misses a dose by more than 12 hours, that dose should be skipped, and the next dose should be taken as scheduled. No double doses should be taken, and dose reductions are not permitted.

On Day 1 of the double-blinded Treatment Period, at the clinic, patients will be given their loading dose of study drug with 8 ounces (240 mL) of room temperature water to facilitate swallowing. Each patient’s mouth will be checked to ensure they have swallowed the tablets. Patients are permitted a light meal prior to arrival at the clinic on Day 1.

On Day 2 to the Week 6 Visit, except for clinic visit days, patients will be instructed to take their daily maintenance dose of study drug before the first meal of the day. Study drug should be taken

with 8 ounces (240 mL) of water and should be taken whole. If a patient misses a dose by more than 12 hours, that dose should be skipped, and the next dose should be taken as scheduled. No double doses should be taken, and dose reductions are not permitted. On the morning of clinic visits, patients are allowed a light meal prior to the visit. For Weeks: 7 through Week 11, the same instructions will be provided to the patient.

The study schema is presented in Figure 5.1-1. Details of study drug administration are provided in Table 7.4-1.

Table 7.4-1 Study Drug Administration

Treatment Group	**Loading Dose (Day 1) ***	**Daily Maintenance Dose (Day 2 Visit to Week 6/EOT/EW) ****
Group 1: LX9211 200 mg*/20 mg**	2 x 50-mg LX9211 tablets + 2 x 50-mg LX9211 tablets	1 x 20-mg LX9211 tablet, qd
Group 2: Placebo	2 x Placebo tablets + 2 x Placebo tablets	1 x Placebo tablet, qd

* Loading dose (Day 1)
** Maintenance dose (Day 2 through – Week 6 Visit)
For Weeks 7 through 11 a single tablet will be taken each day.

7.4.1 Treatment Compliance

Patients will be instructed to bring their study drug bottles, including empty bottles and any unused study drug, to each clinic visit. Pill counts will be performed at each clinic visit by a member of the site staff to determine compliance. Pill count will be recorded on the study drug eCRF.

Treatment compliance (%) will be calculated as:

$$\frac{(\text{Number of tablets dispensed} - \text{Number of tablets returned}) \times 100}{\text{Number of tablets expected to be taken}}$$

The number of tablets expected to be taken is equal to the number of days since the last visit. The Investigator/qualified designee will remind patients at each visit regarding the importance of

taking 1 tablet each morning per protocol. Patients will be deemed “compliant” if their calculated compliance is between 80% and 100%, inclusive. If a patient's compliance is noted to be <80% or >100%, the Investigator will ask the patient for the reason(s) of noncompliance with the dosing instructions, and clearly record the reason(s) in the source documents and on the eCRF and the patient will be reeducated on the need for compliance

If a patient’s compliance is noted to be <80% or >100% on 2 consecutive visits, the patient should be counseled by study personnel, and the Sponsor/designee should be contacted to determine study continuation.

7.5 Dose Adjustment

Dose adjustments of any study drug are not permitted or applicable during the study. For safety reasons, should an unacceptable risk related to study drug arise, patients may be discontinued from the study.

8. Study Procedures

A schedule of study assessments with detailed time points is provided in Appendix A.

8.1 Description of Study Assessments

8.1.1 Patient-reported Outcomes

Three patient-reported outcomes (PROs), ZBPI, PGIC and NPSI, measures will be assessed on a validated electronic device completed at the time of the clinic visit as specified in Appendix A. The ZBPI, a 9-item questionnaire assesses the severity of pain and its impact on functioning in patients with PHN. The PGIC, a 7-point rating scale will assess patient's belief about the overall improvement experienced by the patient at the end of treatment. The NPSI, a 12-item questionnaire, assesses the different components of neuropathic pain syndromes (ie, spontaneous ongoing and paroxysmal pain, evoked pain, paresthesia/dysesthesia). Ten 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.

8.1.2 Qualitative Patient Interview

A telephone qualitative interview substudy will be conducted for approximately 30 patients within 2 weeks following the Week 6 Visit or early withdrawal visit for patients within the US.

The purpose of the phone interview will be to gain insight and understanding of patients' experiences with symptoms of PHN and to assess relevance and clinical meaningfulness of symptom improvements. (eg, reduction in pain).

The qualitative patient interview will be performed as specified in Appendix A.

8.1.3 Clinical Laboratory Assessments

Clinical laboratory assessments will include, at a minimum, blood chemistry (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, and uric acid), lipid panel (high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, triglycerides, creatinine phosphokinase [CPK]), hematology (complete blood count [CBC] with differential, and platelet counts), and urinalysis (including appearance, color, glucose, ketones, nitrite, pH, protein, specific gravity, occult blood, leukocyte esterase, bilirubin, and urobilinogen). Urine microscopy will only be performed if any of the following are present in the urine sample: occult blood, leukocyte esterase, protein, or nitrite. The microscopy will include analysis for the presence of WBC, red blood cells, epithelial cells, bacteria, casts, and crystals.

Additional assessments such as: pregnancy tests [females only]), and a urine screen (drugs of abuse and THC) will be done at time points specified in Appendix A.

The incidence of clinically significant laboratory values, as well as clinically significant shifts in laboratory values, should be reported as an AE (Section 9.1.1) and followed as described in Section 9.5; retests should be performed as frequently as clinically indicated.

8.1.4 Pharmacokinetic Assessments

Plasma samples from all patients will be analyzed for LX9211 C_{p2hr} and C_{trough} levels. Blood draws will be performed at time points indicated in the schedule of events (Appendix A).

[redacted]

8.1.5 Safety Assessments

In addition to the clinical laboratory assessments described in Section 8.1.1, monitoring of AEs is also considered a safety assessment and is described in detail in Section 9. Clinically significant changes compared with Baseline findings for these variables may be reported as AEs on the eCRF. Clinically significant changes compared with Baseline values, which are determined to be AEs should be followed until the event has resolved, the condition has stabilized, etiology of the event is determined to be not related to study drug, or the patient is lost to follow-up. In case a patient reports an AE, study drug may be held for up to 3 days to assess resolution, rather than discontinuing patient permanently from study participation. If the AE improves or resolves, study drug may be resumed. Prior to discontinuing a patient permanently from study participation, the Investigator should discuss the case with the Medical Monitor.

8.1.5.1 Vital Sign Measurements

Measurement of vital signs will include assessment of blood pressure, respiratory rate, pulse rate, and temperature as specified in Appendix A. Vital sign measurements should not be conducted within the 15 minutes immediately following any phlebotomy. Vital signs should be collected with the patient in a seated position.

On Day 1 all patients will have orthostatic BP and HR measured 2 hours after administration of loading dose while in the clinic.

8.1.5.2 Physical Examinations, Height, and Weight

Complete physical examinations will be performed as outlined in Appendix A. A complete physical examination will include, at minimum, a review of the patient's general appearance, head, eyes, ears, nose and throat, neck, heart, lungs, abdomen, back and extremities, skin, and general neurological system.

A symptom-related brief physical exam will only occur if the patient is experiencing symptoms or AEs. If a symptom-related brief physical exam is required, it should include a review of all body systems that relate to the symptoms and/or AE the patient is experiencing.

Height and weight (without shoes) will be measured as outlined in Appendix A. Patients may consume a light meal prior to the visit.

All weights can be taken prior to or after the patient's first meal of the day.

8.1.5.3 Electrocardiograms

Electrocardiograms (ie, 12-lead ECGs) will be performed as specified in Appendix A.

9. Safety Reporting

It is the responsibility of the Investigator to document all AEs and special situations that occur during the study.

Adverse events will be collected at all study visits as outlined in the Schedule of Study Assessments. Each AE should be recorded using the medical diagnosis; if a diagnosis is not established at the time of the reporting, a symptom or sign in standard medical terminology should be used.

Adverse events should not be solicited with leading questions that suggest specific signs or symptoms. Rather, AEs should be solicited by asking the patient a non-leading question such as: "Do you feel different in any way since receiving the dose or since the last assessment?"

Adverse events that occur after the signing of the informed consent and before the first dose of study drug should be recorded as medical history unless the event is a serious adverse event (SAE) that could be associated with the trial procedures and, which could modify the conduct of the trial, or otherwise specified.

9.1 Definitions and Special Considerations

9.1.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Non-serious AE collection will be initiated after the first dose of double-blind study drug.

Any sign, symptom, or illness occurring prior to the first dose of double-blind study drug will be captured in the medical history. Treatment-emergent adverse events are defined as any AEs reported after the first dose of double-blind study drug.

An AE includes any noxious, pathological, or unintended change in anatomical, physiological, or metabolic functions as indicated by physical signs or symptoms occurring after a patient has provided informed consent, whether or not considered related to the study medication.

This definition includes an exacerbation of preexisting medical conditions or events, historical conditions not present prior to study treatment, which reappear following study treatment, intercurrent illnesses, hypersensitivity reactions, drug-drug or drug-food interactions, medication errors, overdose (both intentional or unintentional), drug misuse/abuse, false positive laboratory test, or the significant worsening of the disease under investigation.

Anticipated day-to-day fluctuations of preexisting conditions that do not represent a clinically significant exacerbation or worsening need not be reported as AEs.

Treatment-emergent AEs are defined as any AEs reported after the first dose of double-blind study medication on study Day 1.

Any treatment-emergent abnormal laboratory result should be reported as an AE if it meets 1 or more of the following conditions:

- Fulfills any of the criteria for an SAE (Section 9.1.2),
- Results in discontinuation of study treatment,
- Requires treatment,
- Is considered by the Investigator to be clinically significant.

9.1.1.1 Special Considerations for Bladder Dysfunction-related Adverse Events

In studies with LX9211 in dogs, changes to the urinary bladder (including minimal inflammation, slight urothelial hyperplasia, minimal focal ulceration, and minimal muscle degeneration) were noted. The doses used in these animal studies were much higher than what will be used in this Phase 2. In the Phase 1 SAD and MAD studies with LX9211, no clinically significant CMP, UA findings, or bladder dysfunction-related AEs were reported in any subject.

In this study, bladder dysfunction-related AEs will be closely monitored on an ongoing basis. In addition, an unscheduled visit may be conducted in case of a reported AE suspicious for urinary bladder abnormalities, where additional labs and follow-up may be obtained, as deemed necessary.

9.1.2 Serious Adverse Events

All SAEs will be collected starting with signing informed consent and continue until 35 days after the last dose of study drug.

An SAE is defined as any AE that results in any of the following outcomes:

- Death;
- A life-threatening AE - defined as an event, in the view of the Investigator, the occurrence of which places the patient or patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death;
- Hospitalization or prolonging of an existing hospitalization;

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or,
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Hospitalization is defined as any inpatient overnight stay in a hospital. This does not include an emergency room visit or admission to an outpatient facility.

A hospitalization in and of itself should not be reported as an SAE.

Hospitalizations for preplanned or elective surgery or routine clinical procedures without worsening of the underlying condition, or for administrative/social reasons (such as convenience, logistics) should not be reported as SAEs. However, if an elective procedure has to be performed sooner than planned due to a worsening of the underlying medical condition and the patient is hospitalized for the procedure, the worsening medical condition should be reported as an SAE.

Any laboratory abnormality fulfilling any of the criteria for an SAE should be reported as such.

9.1.3 Unexpected Adverse Events

An unexpected AE is an AE that is not listed in the Reference Safety Information (eg, the IB) or is not listed at the specificity or severity that has been observed. “Unexpected” also refers to the AEs that are mentioned in the Reference Safety Information as occurring with the class of study medication or as anticipated from the pharmacological properties of the study medication, but are not specifically mentioned as occurring with the study medication.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents.

It the responsibility of the Sponsor to assess whether an AE is expected or unexpected.

9.2 Assessment of Adverse Events

The Investigator will evaluate all AEs with regard to the severity and relationship to study drug.

9.2.1 Severity

The Investigator will assess the severity of each AE using their clinical expertise and judgment using 1 of the following 3 severity grades:

- **Mild**: event is transient and easily tolerated, and requires no or minimal treatment
- **Moderate**: event causes limited interference with usual daily activity and requires simple therapeutic intervention
- **Severe**: event causes marked interference with usual daily activities and requires systemic drug therapy or other therapeutic intervention

Changes in the severity of an AE should be documented as separate AEs to allow an assessment of the duration of the event at each level of severity.

9.2.2 Causality

Causality assessment is a determination of whether there is a reasonable possibility that the study medication caused an AE. Factors that should be considered in causality assessment include, but are not limited to, temporal relationship, dechallenge/rechallenge information, association (or lack of association) with underlying disease or concomitant medication, biological plausibility, and previous observation or lack of with the study medication or other medication(s) in the same class as the study medication.

For each AE, the Investigator will assess the causal relationship between the study medication and the AE using their clinical expertise and judgment according to the most appropriate description as follows:

- **Not related**: The AE does not follow a reasonable temporal relationship to administration of the study medication, or an alternative etiology (eg, underlying disease, complications, concomitant drugs, or concurrent treatment) is much more likely
- **Unlikely related**: The AE has an improbable temporal relationship to administration of the study medication, or an alternative etiology (eg, underlying disease, complications, concomitant drugs, or concurrent treatment) is more likely

- **Possibly related**: The AE follows a reasonable temporal relationship to administration of the study medication (including the course after withdrawal of the drug), and an alternative etiology (eg, underlying disease, complications, concomitant drugs, or concurrent treatment) is equally or less likely
- **Probably related**: The AE follows a reasonable temporal relationship to administration of the study drug (including the course after withdrawal of the drug), and an alternative explanation (eg, underlying disease, complications, concomitant drugs, or concurrent treatment) is unlikely
- **Definitely related**: The AE follows a plausible temporal relationship to administration of the study medication (including the course after withdrawal of the drug) and alternative etiology (eg, underlying disease, complications, concomitant drugs, or concurrent treatment) can be ruled out. Positive rechallenge (ie, reappearance or worsening of the AE after the study drug is reintroduced) or a response pattern known to be associated with administration of the study drug provides further evidence of a definitive causality assessment.

9.3 Special Situations

Unless otherwise defined, events described below should be reported in the manner and timeframe as SAEs (Section 9.4)

9.3.1 Pregnancy

Any patient who becomes pregnant during the study must be discontinued from the study immediately.

Any pregnancy during the study that occurs after administration of the study medication, where the embryo or fetus may have been exposed to the study medication (either through maternal exposure or transmission of a medicinal product via semen following paternal exposure), should be followed-up in order to collect information on the outcome of the pregnancy and development of the child after birth.

The pregnancy exposure should be reported on the Pregnancy Form (initial notification form) and captured on the eCRF page for AEs. The pregnant woman should be followed for pregnancy outcome through delivery or termination of the pregnancy. In pregnancies that progress to term, the infants should be followed till 6 months after birth and any congenital abnormalities/birth defects in the infants should be reported as an SAE.

The outcome of a pregnancy, and the presence or absence of a congenital abnormality should be reported on the Pregnancy Form (outcome form).

After the study period, pregnancies should be collected by requesting study patients notify the Investigator if a female patient or a female partner of a male patient becomes pregnant within 35 days after last dose of study medication. These pregnancies should be reported and followed in the same manner as pregnancies occurring during the study.

9.3.2 Adverse Events of Special Interest

No AEs of special interest have been defined for this study.

9.4 Reporting of Serious Adverse Events and Pregnancies

All SAEs, regardless of causal relationship to the study medication, and pregnancies must be reported to the Sponsor within 24 hours of investigational site awareness of the event. Investigators should not wait for complete information on an event before notifying the Sponsor (or designee) of an SAE.

Investigational site personnel must use the SAE Report form and Pregnancy form provided by the Sponsor to report these events.

The SAE form should be sent to:

Safety Data Facsimile: (832) 442-5462 or
Email address (in case of fax failure): drugsafetygeneral@LexPharma.comm

In case of failure of/lack of access to both email and fax, the event should be reported using Safety Hotline: (877) 372-3597.

If an SAE is reported via telephone, the telephone report should be followed by a completed SAE Report form.

For questions on safety reporting, the Safety Physician of the study should be contacted at:

[redacted] MD
[redacted]
Email: [redacted]
Telephone: [redacted]

For questions on study patient management related to AEs, the Medical Monitor of the study should be contacted.

[redacted], MD

[redacted]
Email: [redacted]
Telephone: [redacted]

Where applicable, information from relevant hospital records and autopsy reports should be obtained.

Additional information received after the initial SAE has been reported to the Sponsor should be reported as follow-up information following the same procedure and timeline as the initial SAE.

All SAEs, pregnancies, and other special situations should also be recorded on the study patient's eCRF page for AEs.

An SAE that occurs after completion of the study and in the opinion of the Investigator, is related to the study medication should be reported following the same procedure and timeline as an SAE that occurs during the study.

9.5 Follow-up of Adverse Events

All AEs should be followed until the event has resolved, the condition has stabilized, the patient is lost to follow-up, or ≥35 days following the last dose of study drug, whichever comes first. Final known outcome must be reported whenever possible.

Medically significant abnormal laboratory test results should be repeated and followed until the test results have returned to the normal range or Baseline value, and/or an adequate explanation of the abnormality is determined.

9.6 Safety Oversight

A DMC will be utilized for this study.

10. Statistical Methodology

10.1 Determination of Sample Size

Proposed Sample Size

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 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 standard deviation 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 H_1 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 approximately the 50% information time 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 $\alpha = 0.025$ 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 efficacy 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]

10.2 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.

10.2.1 Intent-to-Treat (ITT) Population

The ITT population will include all randomized patients.

10.2.2 Modified Intent-to-Treat (mITT) Population

The mITT population will include all randomized patients who have taken ≥1 dose of study drug.

10.2.3 Per Protocol (PP)

The PP population will include patients in the mITT population who did not have any major deviations that would interfere with the collection or interpretation of the efficacy data.

10.2.4 Pharmacokinetics Population (PK)

10.2.4.1 Pharmacokinetics Population (PK) – C_{trough}

The PK population for evaluation of C_{p2hr} and C_{trough} will include all patients who received ≥1 dose of study drug and ≥1 sample collected.

10.2.5 Safety Population

The Safety Population is defined as those patients who received any exposure to study drug.

10.3 Study Endpoints

10.3.1 Primary Efficacy Endpoint

The change from Baseline (Week 2 of the Run-in Period) to Week 6 in Average Daily Pain Score (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])

10.3.2 Secondary Efficacy Endpoints

- 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 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.

10.3.3 Other Efficacy Endpoints

Other efficacy endpoints are:

- Change from Baseline to Week 6 in the Neuropathic Pain Symptom Inventory (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

10.3.4 Pharmacokinetic (PK) / Pharmacodynamic (PD) Endpoint

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

[redacted]

10.3.5 Safety Endpoints

Safety endpoints are as follows:

- Incidence of treatment-emergent AEs, suspected adverse reaction, AEs leading to discontinuation from the study, 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 PE findings
- Actual and change from Baseline in ECG findings

10.4 Statistical Methods

Continuous variables (including C_{trough}) will be summarized by the mean, standard deviation, median, minimum, and maximum values for all patients with non-missing data. Categorical variables will be summarized by their counts and associated percentages. All data will be provided in individual patient listings. A formal SAP with more details on the statistical methods will be completed prior to database lock and unblinding of the study data.

10.4.1 Extent of Study Drug Exposure and Compliance

The extent of study treatment exposure and compliance will be assessed and summarized by actual treatment received in the safety population.

10.4.1.1 Extent of Study Drug Exposure

The extent of study treatment exposure will be assessed by the duration of treatment exposure during the study. The duration of treatment exposure will be the total number of days of administration of the study drug, regardless of unplanned intermittent discontinuations. The

duration of study drug exposure will be calculated as: (Date of the last study drug taken – Date of the first study drug taken) + 1.

Descriptive statistics of duration of treatment exposure (number, mean, SD, minimum, median, and maximum) will be presented by treatment group. The number and percentage (%) of patients randomized and exposed to the study drug will be presented by visit/week for each treatment group.

10.4.1.2 Compliance

A patient will be considered noncompliant if they did not take the planned dose of treatment as required by the protocol. Treatment compliance will be summarized descriptively (number, mean, SD, median, minimum, and maximum). The percentage of patients with overall compliance <80% will be summarized descriptively by treatment group.

10.4.2 Analyses of Efficacy Endpoints

All efficacy analyses will be performed on the mITT population as defined in Section 10.2.2. Supportive analyses will be performed on the PP population.

10.4.2.1 Analysis of Primary Efficacy Endpoint

The primary endpoint is the change from Baseline to Week 6 in ADPS. 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, provide that ≥5 days from that period are available for analysis. The Week 6 mean value will be derived from the 7-day period immediate to the endpoint, provided that ≥4 days of non-missing data are collected.

A restricted maximum likelihood-based, mixed-effects model repeated measures (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, and the Baseline score as 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. In the event that a rescue medication is used, a supplementary MMRM model will be applied to a dataset that excludes data collected after the initiation of the rescue medication. To assess the robustness of the MMRM analyses performed under the missing at random (MAR) assumption, and given the long half-life of LX9211, pattern mixture models (PMM) with copy reference-based imputation methods will be applied to both datasets (with and

without data collected after the initiation of the rescue medication). The imputed datasets will be combined by use of Rubin's rule and analyzed using an analysis of covariance (ANCOVA) model fitted for the fixed effects of treatment, the randomization stratum of Baseline pain severity, and the continuous fixed covariate of Baseline score.

10.4.2.2 Analysis of Secondary and Other Efficacy Endpoints

Continuous secondary and other efficacy endpoints: ZBPI scores, PGIC scores and NPSI scores, measured at multiple time points, will be analyzed using a similar modeling strategy as used for the primary endpoint.

Categorical secondary endpoints: The proportion of responders based on Question 5 of ZBPI will be compared between treatment groups using a Cochran-Mantel-Haenszel test stratified by the randomization factor of Baseline pain severity. Patients with missing measurement at Week 6 will be considered non-responders. A nonresponder imputation (NRI) rule will be applied for all analyses based on categorical variables to assign outcomes to missing observations. The percentage of patients who need rescue medication and prematurely dropout will be summarized descriptively. The Kaplan-Meier methods 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 and Week 11.

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

10.4.2.3. Multiplicity

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.

10.4.3 Pharmacokinetic (PK)/ Pharmacodynamic (PD) Analyses

PK plasma concentration data will be summarized descriptively by dose and nominal time point. All PK data will be presented in the data listings. [redacted]

10.4.4 Subgroup Analyses

The primary endpoint will be analyzed by the following subgroup of population

- Baseline pain severity moderate or severe
- Sex

Additional subgroup analyses may be conducted and will be described in the SAP. All subgroup analyses will be exploratory.

10.4.5 Safety Analyses

All safety analyses will be performed on the Safety population as defined in Section 10.2.5.

Safety will be assessed by evaluating all reported adverse events, actual and changes in clinical laboratory values, vital signs, and ECGs. Baseline for computing the change in safety variables will be the observation measured before the first dose (Day 1). No formal statistical significance tests will be performed on safety data.

10.4.5.1 Adverse Events

Adverse events verbatim descriptions (Investigator terms from the eCRF) will be coded using the Medical Dictionary for Regulatory Activities MedDRA, Version 23.

Treatment emergent adverse events (TEAEs) are defined as events that first occurred or worsened after the first dose (Day 1). Treatment-related adverse events are defined as events that are indicated on the CRF by the Investigator to be treatment related.

Incidence of TEAEs will be summarized descriptively by PT within each SOC and presented by treatment group and as needed, by study time point. Treatment-emergent adverse event (TEAE) summaries will include the overall incidence of TEAEs, Incidence of TEAEs (by System Organ Class [SOC] and Preferred Term [PT]), TEAEs by maximum intensity (mild, moderate, or severe), TEAEs by relationship to study treatment (related, or unrelated). In addition, events leading to discontinuation of study drug, deaths, and SAEs will also be summarized and/or listed by patient. If a patient reports the occurrence of a particular event more than once, the most severe of that event will be counted in the summary of the TEAEs, and the greatest degree of relationship to treatment will be included in the summary of treatment-related events. Patients will be counted only once within a SOC and PT, even if the patient experienced more than 1 TEAE within a specific SOC or PT. A by-patient data listing of all AEs will be provided.

10.4.5.2 Deaths, Serious and Other Significant Adverse Events

Listings of all deaths, SAEs, and AEs leading to discontinuation from study treatment will be provided.

10.4.5.3 Clinical Laboratory Parameters

Laboratory results will be reported in conventional units and Systeme International (SI) units. Clinical laboratory value observed at Baseline (predose), at each time point, and changes from Baseline to each assessment time point will be summarized using descriptive statistics and presented by treatment group. Additionally, each patient's laboratory results will also be classified as low, normal, or high according to standard normal ranges and summarized using shift tables, comparing the Baseline and each assessment time point. Percentages will be based on the number of patients with both non-missing Baseline and relevant postBaseline results. A by-patient data listing of all clinical laboratories will be provided.

10.4.5.4 Vital Signs

Vital signs values, and changes from Baseline will be summarized using descriptive statistics and presented by treatment group. In addition, vital signs categorized as "clinically significant (CS)" or "not clinically significant (NCS)" will be summarized descriptively and presented by treatment group in shift tables. A by-patient data listing of all vital signs' parameters will be provided.

10.4.5.5 Physical Examination Findings

Physical examination findings will be listed for each patient.

10.4.5.6 Electrocardiogram (ECG)

The actual values of the 12-lead ECG parameters at Baseline, at each time point, and change from Baseline will be summarized using descriptive statistics. The number and percentage of patients with ≥1 postBaseline abnormal ECG result will be summarized using descriptive statistics and presented by treatment group.

10.4.5.7 Interim Analysis

An interim analysis of the primary endpoint will be performed to test for futility when approximately 50% of the planned information has been achieved. This will occur when the first 38 patients have been accrued and followed to endpoint at Week 6 or dropped out from the trial earlier, whichever event occurs first. Should a patient drop out early in the study, but return for the Week 6 visit, that 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 ratio.

A non-blinding 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 $\alpha = 0.05$). 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).

Details of the futility analysis will be described in the SAP and DMC Charter documents.

10.4.6 Baseline Characteristics and Other Summaries

Treatment group differences will be summarized descriptively for demographic data, prior and concomitant medications, treatment compliance, and final disposition.

10.4.6.1 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Study Manual requirements. The noncompliance may be either on the part of the patient, the Investigator, or the study site staff.

Significant deviations (ie, those categorized as critical or major) will be provided as listings in the final report.

11. Study Management

The Investigator is responsible for completing and maintaining adequate and accurate eCRFs and source documentation. Source documentation constitutes original records, which may include: progress notes, medication administration records, laboratory reports, ECG tracings, discharge summaries, etc.

It is the responsibility of the Investigator and site staff to use continuous vigilance to identify and report deviations. In addition to notifying the Sponsor, protocol deviations are to be reported to the Institutional Review Board (IRB) as per applicable guidelines. The Investigator and site study staff are responsible for knowing and adhering to their IRB requirements.

All data and corrections, if applicable, entered on to the eCRF must meet minimum requirements as specified in the case report form guidelines. All eCRFs should be completed in their entirety

and stored in accordance with ICH GCP guidelines. The Investigator must sign the Investigator's statement in each patient's eCRF indicating that the data reported are accurate.

At the study site, clinical research associates will verify up to 100% of eCRFs in their entirety against source documentation. Computer programmed edit checks will be run against the database to check for discrepancies and reasonableness of the data, and the safety database will be reconciled with the clinical database. All issues resulting from the computer-generated checks and the safety database reconciliation will be resolved according to standard data management practices in conjunction with the Sponsor, clinical study personnel, and the study Investigators.

11.1 Monitoring

The Sponsor is responsible for ensuring the proper conduct of the study with regard to ethics, protocol adherence, site procedures, integrity of the data, and applicable laws and/or regulations. At regular intervals during the study and following completion of the study, the Sponsor's study monitors will contact the study site via visits to the site, telephone calls, and/or letters in order to review study progress, eCRF completion, and address any concerns or questions regarding the study conduct. During monitoring visits, the following aspects of study conduct will be carefully reviewed: informed consent of patients, patient recruitment, patient compliance with the study procedures, source data verification, drug accountability, use of concomitant therapy by patients, AE and SAE documentation and reporting, and quality of data. Records pertaining to these aspects are expected to be kept current.

The Investigator must make study data accessible to the clinical monitor, to other authorized representatives of the Sponsor, and to regulatory inspectors.

11.2 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Study Manual requirements. The noncompliance may be either on the part of the patient, the Investigator, or the study site staff.

It is the responsibility of the Investigator and site staff to use continuous vigilance to identify and report deviations. In addition to notifying the Sponsor, protocol deviations are to be reported to the Institutional Review Board (IRB) as per applicable guidelines. The Investigator and site study staff are responsible for knowing and adhering to their IRB requirements.

Study clinical research associates will record deviations identified by the site and those identified during their review of study documentation in a tracking system for assessment and for ensuring proper follow-up and remediation, as required.

In the case of certain deviations, including those that are deemed to be Critical or Major, corrective actions may need to be developed by the site (with the input of the Sponsor/CRO), and implemented promptly. Prospective requests to deviate from the protocol (ie, waivers) will not be approved unless the approval is required to protect the health or welfare of the patients enrolled in the study.

11.3 Audits and Inspections

The Sponsor, regulatory authority, or IRB may visit the study site at any time during the study or after completion of the study to perform audits or inspections. The purpose of a Sponsor audit or regulatory inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted according to the protocol, GCP, ICH guidelines, and any other applicable regulatory requirements. Investigators should contact the Sponsor immediately if contacted by a regulatory agency about an inspection at their site.

11.4 Amendments

Any amendments to the protocol will be written and approved by the Sponsor. All amendments must be submitted to the IRB for approval prior to implementing the changes. In some instances, an amendment may require changes to the informed consent form, which also must be submitted for IRB approval prior to administration to patients. If any changes to the eCRF are required, the Sponsor will issue supplemental or revised eCRF pages.

11.5 Record Keeping

11.5.1 Drug Accountability

The Investigator must maintain accurate records of study drug receipt, dispensing information, and disposition. If the Investigator cannot account for all clinical supplies at the termination of the study, a written explanation must be provided.

11.5.2 Health Insurance Portability Accountability Act of 1996 and Subsequent Updates

The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of patient health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation and any applicable updates). The Investigator shall ensure that study patients authorize the use and

disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.

The Department of Health and Human Services updated a final rule to modify HIPAA. The new rule has been in effect since 26 Mar 2013, and strengthens the privacy and security protection for individual's health information; modify the rule for Breach Notification for Unsecured Protected Health Information (Breach Notification Rule) under the HITECH Act to address public comment received on the interim final rule; modify the HIPAA Privacy Rule to strengthen the privacy protections for genetic information by implementing section 105 of Title I of the Genetic Information Nondiscrimination Act of 2008 (GINA); and make certain other modifications to the HIPAA Privacy, Security, Breach Notification, and Enforcement Rules (the HIPAA Rules) to improve their workability and effectiveness and to increase the flexibility for and decrease burden on the regulated entities.

The full text of the rule can be found at:
https://www.federalregister.gov/documents/2013/01/25/2013-01073/modifications-to-the-hipaa-privacy-security-enforcement-and-breach-notification-rules-under-the

11.5.3 Financial Disclosure

The Investigator shall provide to the Sponsor sufficient accurate financial information to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the FDA. The Investigator shall promptly update this information if any relevant changes occur in the course of the study or for 1 year following completion of the study.

11.5.4 Access to Original Records

It is an expectation of regulatory authorities that monitors, auditors, and representatives of national and international government regulatory agency bodies have access to original source documentation (see examples in Section 11) to ensure data integrity. "Original" in this context is defined as the first documentation of an observation and does not differentiate between hard copy and electronic records.

11.5.5 Retention of Study Documents

The EU clinical trial regulation (Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 (Article 58) mandates a minimum retention period for the trial master file of "25 years after the end of the clinical trial". This establishes a more specific time period than with internationally accepted practice of ICH GCP.

The Investigator must not destroy any study-related records without receiving approval from the Sponsor. The Investigator must notify the Sponsor in the event of accidental loss or destruction of any study records. If the Investigator leaves the institution where the study was conducted, the Sponsor must be contacted to arrange alternative record storage options.

12. Administrative Structure of the Study

The study will be monitored by Sponsor personnel or Sponsor representative. The following functions including, but not limited to data management, statistical analysis, including PK analysis, and reporting may be performed by organizations designated by the Sponsor. Specific functions designated by the Sponsor to an organization are to be defined via a formal transfer of obligations document.

13. Appendix A – 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 postdose)	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 patient'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.

14. Appendix B – Amount of Blood to be Collected from Each Patient

Estimated Amount of Blood Volume to be Collected from Each Patient											
Procedure	**Screening**	**Single-blind Placebo Run-in Period**	**Double-blind Treatment Period**					**Follow-up**	**Total # of Tests**	**Volume/Test (mL)**	**Total Volume (mL)**
	Week -4	**Week -2**	**Day 1**	**Week 2**		**Week 4**	**Week 6**	**Week 11**			
Serum pregnancy	1								1	2	2
Hematology and chemistry	1		1				1		3	9	27
C_{trough} blood samples			1	1		1	1	1	5	4	20
C_{p2hr} blood samples			1						1	4	4
[redacted]											
									TOTAL		**88**

15. Appendix C – Ethical Standards

Ethics and Regulatory Considerations

This study will be conducted according to GCP, 21 CFR Part 50, (Protection of Human Subjects), 21 CFR Part 56 (Institutional Review Boards), International Conference on Harmonisation Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance, the Nuremberg Code, and the Declaration of Helsinki.

General Instructions

The FDA regulates studies of drugs, biologics, and medical devices. Consequently, these studies are subject to GCP regulations and guidance issued by the FDA and are included in, but not limited to, the following parts of the CFR and guideline document:

- 21 CFR Part 11 – Electronic Records
- 21 CFR Part 50 – Protection of Human Subjects
- 21 CFR Part 54 – Financial Disclosure
- 21 CFR Part 56 – Institutional Review Boards
- 21 CFR Part 312 – Investigational New Drug Application
- Current FDA Guideline for the Monitoring of Clinical Investigations
- Current Guidance for Institutional Review Boards and Clinical Investigators
- ICH E6 – Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance

Copies of these materials are available from the Sponsor upon request. The purpose of these regulations and legal obligations is to define the standards and principles for the proper conduct of clinical trials that have been developed by the medical, scientific, and regulatory communities. They are not intended to impede or restrict clinical research.

The ethical standards defined within GCP are intended to ensure that:

- human subjects are provided with an adequate understanding of the possible risks of their participation in the study, and that they have a free choice to participate or not;
- the study is conducted with diligence and in conformance with the protocol in such a way as to ensure the integrity of the findings; and
- the potential benefits of the research justify the risks.

Lexicon Pharmaceuticals, Inc., is the Sponsor of the Investigational New Drug Application (IND). The Sponsor is responsible for the following:

- selecting qualified Investigators,
- providing Investigators with the information they need to properly conduct an investigation,
- ensuring proper monitoring of the investigation,
- ensuring that the study is conducted according to the general investigational plan and protocols contained in the IND,
- maintaining the IND, and
- ensuring that FDA and all participating Investigators are properly informed of significant new information regarding adverse effects or risks associated with the drug being studied.

16. Appendix D – Investigator Obligations

Per Title 21 of the US Government Code of Federal Regulations (21 CFR) Parts 50 and 56, the study protocol and the final version of the subject informed consent form will be approved by the institutional review board (IRB) before enrollment of any subjects. The opinion of the IRB will be dated and given in writing. A copy of the letter of approval from the IRB and a copy of the approved informed consent form will be received by the Sponsor prior to shipment of study drug supplies to the Investigator.

The Investigator will ensure that the IRB will be promptly informed of all changes in the research activity and of all unanticipated problems including risk to subjects. The Investigator will also ensure that no changes will be made to the protocol without IRB approval.

As a part of the IRB requirement for continuing review of approved research, the Investigator will be responsible for submitting periodic progress reports to the IRB at intervals appropriate to the degree of subject risk involved, but no less than once per year.

Written informed consent must be given freely and obtained from every subject prior to clinical trial participation. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

As described in GCP guidelines, study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). Study personnel will not include individuals against whom sanctions have been invoked after scientific misconduct or fraud (eg, loss of medical licensure, debarment). Quality assurance systems and procedures will be implemented to assure the quality of every aspect of the study.

Principal Investigators in the US must provide the Sponsor with a fully executed Form FDA 1572 (statement of Investigator) and all updates on a new fully executed Form FDA 1572.

Principal Investigators must provide the Sponsor with their own curriculum vitae and current curriculum vitae for each sub Investigator listed on the Form FDA 1572.

<u>Protection of Human Subjects (21 CFR Part 50)</u>

Informed consent must be obtained from every subject before entry into a clinical study. It must be given freely and not under duress. Consent must be documented by use of an IRB-approved consent form and signed by the subject or the subject's legally authorized representative. The Department of Health and Human Services suggests that when minors are involved, a parent or guardian should sign the consent form. If the minor is an adolescent,

their signature should also be included. Non-English-speaking subjects must be presented with a consent form written in a language that they understand. A copy of the signed consent form must be given to the subject signing it. Another copy must be kept in the Investigator's files and made available to FDA representatives upon request. If, for any reason, subject risk is increased as the study progresses, a revised, IRB-approved consent form must be signed by the subject. Before the study begins, a sample of the consent form must be provided to the Sponsor for review. The FDA may reject otherwise scientifically valid studies if proper informed consent has not been obtained from all subjects.

Only in the case of a life-threatening incident may an investigational product be used without prior signed consent. In such an emergency situation, separate certifications must be written both by a physician not participating in the study and by the Investigator. The certifications, along with the protocol and informed consent, must be sent to the IRB within 5 working days. In this situation, the Investigator may not administer any subsequent product to that subject until informed consent and IRB approval are obtained.

Informed Consent

Written informed consent must be obtained from each subject prior to entry in the study. One copy of the signed informed consent document will be given to the subject, and another will be retained by the Investigator. Additionally, the patient must be allowed adequate time to consider the potential risks and benefits associated with their participation in the study.

In situations where the patient is not legally competent to provide consent (ie, mentally incapacitated), written consent must be obtained from a parent, legal guardian, or legal representative. In these situations, the consent must be signed and dated by a witness.

The informed consent document must have been reviewed and approved by the Sponsor and by the Investigator's IRB prior to the initiation of the study. The document must contain the 8 basic elements of informed consent and may contain the 6 additional elements described in 21 CFR Part 50. Every consent form must include the following 8 elements:

- A statement that the study involves research, an explanation of the purpose of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental
- A description of any reasonably foreseeable risks or discomforts to the subject
- A description of any benefits to the subject or to others that may reasonably be expected from the research

- A disclosure of appropriate alternative procedures or course of treatment, if any, that might be advantageous to the subject
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and noting the possibility that the FDA and representatives may inspect the records
- An explanation as to whether any compensation or medical treatments are available if injury occurs for research involving more than minimal risk. The explanation should involve a description of the compensation or treatment available, or a statement describing where further information may be obtained
- An explanation of whom to contact for answers to pertinent questions about the research and the subject's rights and whom to contact in the event of a research related injury
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

When appropriate, 1 or more of the following elements of information shall also be included in the consent form:

- A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant), which are currently unforeseeable
- Anticipated circumstances under which the subject's participation may be terminated by the Investigator without regard to the subject's consent
- Any additional costs the subject may incur from participation in the research
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject
- A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject
- The approximate number of subjects involved in the study

The Declaration of Helsinki includes further details regarding the specific requirements for informed consent.

Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable federal, state, or local laws.

The informed consent requirements in these regulations are not intended to preempt any applicable federal, state, or local laws that require additional information to be disclosed in order that informed consent be legally effective. Some states, such as California and Oregon, require further action on the Investigator's part concerning subject consent.

Study Documentation

Institutional Review Board (IRB) Ethic Review Committee (ERC) Review/Approval

The protocol and informed consent for this study, including advertisements used to recruit patients, must be reviewed and approved by an appropriate IRB/ERC prior to enrollment of patients in the study. It is the responsibility of the Investigator to assure that all aspects of the ethical review are conducted in accordance with the current Declaration of Helsinki, ICH, GCP, and/or local laws, whichever provide the greatest level of protection. A letter documenting the IRB/ERC approval, which specifically identifies the study/protocol and a list of the committee members must be received by the Sponsor prior to initiation of the study. Amendments to the protocol will be subject to the same requirements as the original protocol.

A progress report with a request for reevaluation and reapproval will be submitted by the Investigator to the IRB/ERC at intervals required by the IRB/ERC, and not less than annually. A copy of the report will be sent to the Sponsor.

When the Sponsor provides the Investigator with a Safety Report, the Investigator must promptly forward a copy to the IRB/ERC.

After completion or termination of the study, the Investigator will submit a final report to the IRB/ERC and to the Sponsor, if required. This report should include: deviations from the protocol, the number and types of patients evaluated, the number of patients who discontinued (with reasons), results of the study, if known, and significant AEs, including deaths.

Study Files

The Investigator is required to maintain complete and accurate study documentation in compliance with current Good Clinical Practice standards and all applicable federal, state, and local laws, rules, and regulations related to the conduct of a clinical study. Study documents include, but are not limited to, the Investigator's Brochure, drug accountability

records, Sponsor/Investigator correspondence, IRB correspondence, protocol and amendments, information regarding monitoring activities, subject exclusion records, CRFs, and data queries.

Confidentiality

The anonymity of participating subjects must be maintained. Subjects will be identified by their initials and an assigned subject number on CRFs and other documents submitted to the clinical monitor. Documents that will be submitted to the clinical monitor and that identify the subject (eg, the signed informed consent document) must be maintained in strict confidence by the Principal Investigator, except to the extent necessary to allow auditing by the FDA, the clinical monitor, or Sponsor personnel.

All information regarding the nature of the proposed investigation provided by the Sponsor to the Investigator (with the exception of information required by law or regulations to be disclosed to the IRB, the subject, or the FDA) must be kept in confidence by the Investigator.

Drug Accountability

The Investigator or designee is responsible for accountability of the investigational product at the site. The Investigator or designee must maintain records of the product's delivery to the site, inventory at the site, use by each subject, and return to the Sponsor or alternative disposition of any unused product. These records must include dates, quantities, batch/serial/lot numbers, and expiration dates (if applicable).

The Investigator should ensure that the investigational product is used only in accordance with the protocol.

17. Appendix E – Calculations

Cockcroft-Gault equation:

The equation for calculation of creatinine clearance, as an estimation of glomerular filtration rate (eGFR), using the method of Cockcroft and Gault is:

$$\frac{[(140-age) \times weight\ (in\ kg)]}{[72 \times serum\ creatinine\ (in\ mg/dL)]}$$

If the patient is female, multiply the above by 0.85

For an online calculator, please use: http://www.nephron.com/cgi-bin/CGSI.cgi

Source: Cockcroft D, Gault MD. Prediction of Creatinine Clearance from Serum Creatinine. Nephron. 1976;16:31-41.

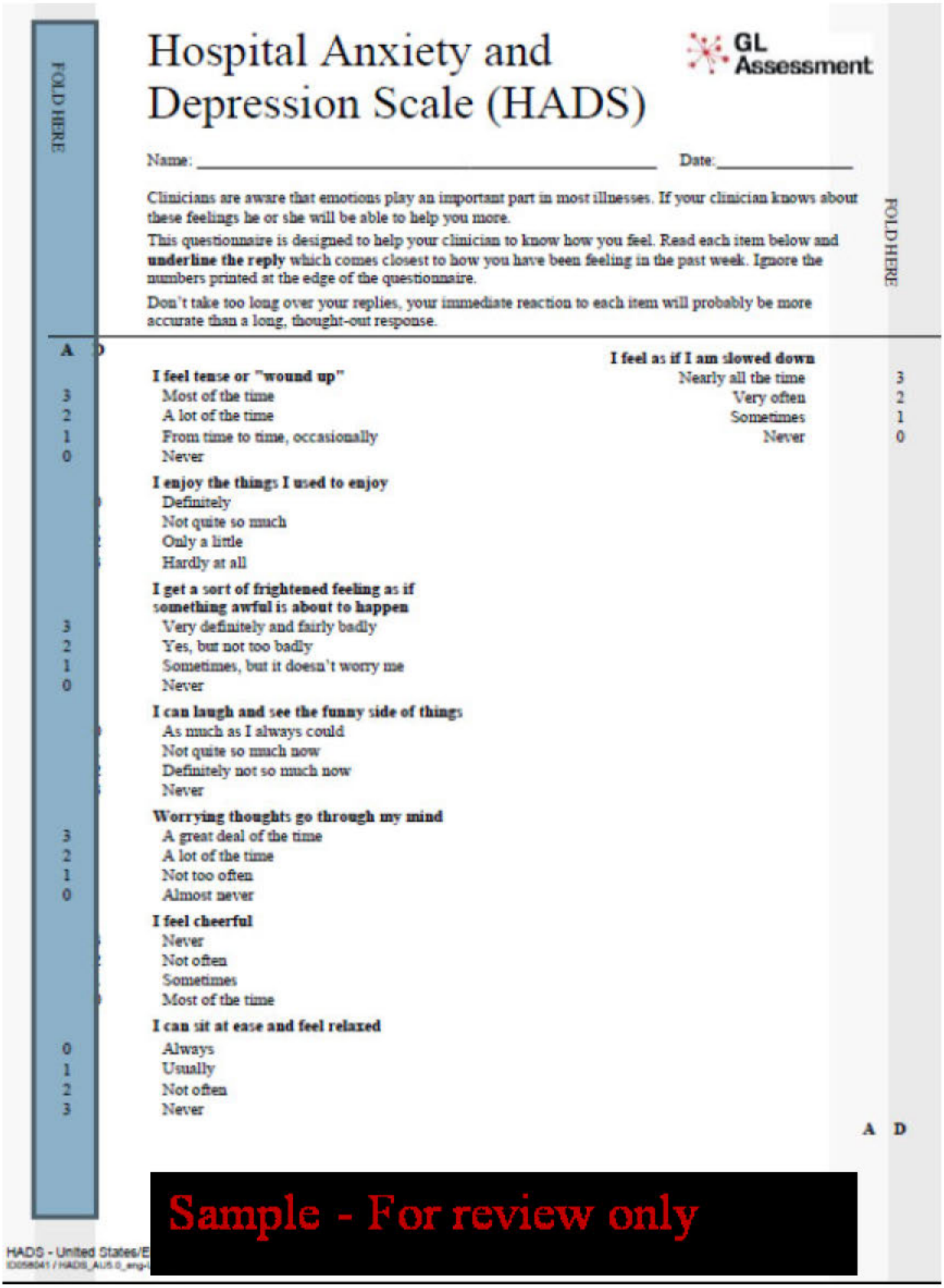
Body Mass Index equation:

Measurement Units	Formula and Calculation
Kilograms and meters (or centimeters)	Formula: weight (kg) / [height (m)]^2 With the metric system, the formula for BMI is weight in kilograms divided by height in meters squared. Since height is commonly measured in centimeters, divide height in centimeters by 100 to obtain height in meters. Example: Weight = 68 kg, Height = 165 cm (1.65 m) Calculation: 68 ÷ (1.65)^2 = 24.98
Pounds and inches	Formula: weight (lb) / [height (in)]^2 x 703 Calculate BMI by dividing weight in pounds (lbs) by height in inches (in) squared and multiplying by a conversion factor of 703. Example: Weight = 150 lbs, Height = 5'5" (65") Calculation: [150 ÷ (65)^2] x 703 = 24.96

For an online calculator, please use:
http://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/english_bmi_calculator/bmi_calculator.html for feet, inches, and pounds and
http://www.cdc.gov/healthyweight/assessing/bmi/adult_BMI/metric_bmi_calculator/bmi_calculator.html for meters and kilograms

From the Centers for Disease Control and Prevention site:
http://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html#Interpreted

18. Appendix F – 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 D

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
- 3 Nearly all the time
- 2 Very often
- 1 Sometimes
- 0 Never

A D

Sample - For review only

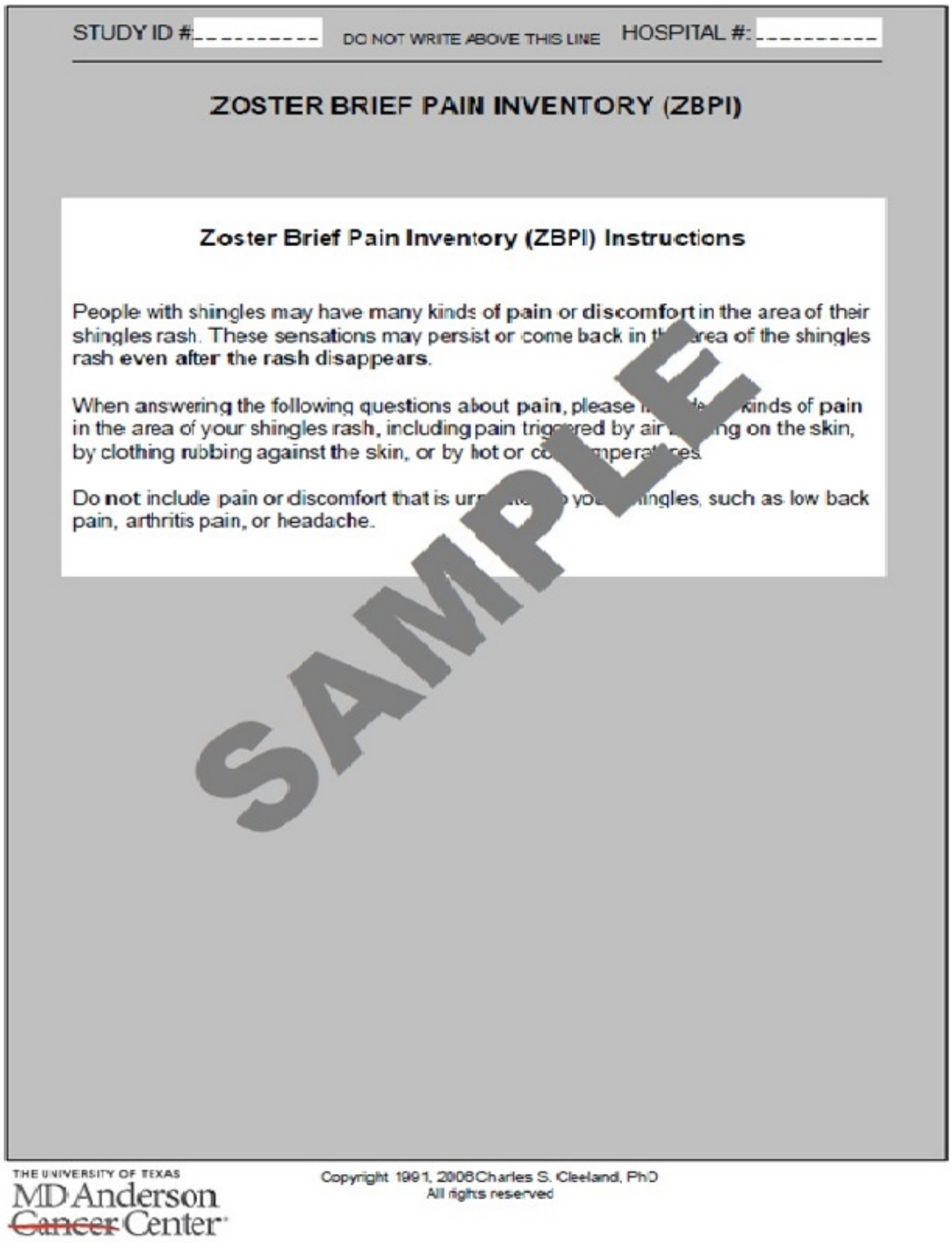
HADS - United States/E
ID058041 / HADS_AUS.0_eng-

	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.

	A	D
TOTAL		

19. Appendix G – 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)

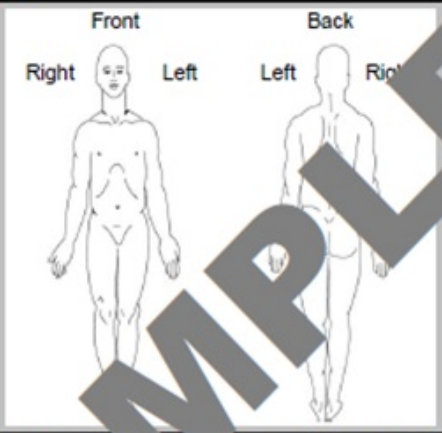
Date: ____/____/_____ **Time:** _____

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

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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

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20. Appendix H – 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-G_TG1.0_ID2006-2007_eng-USori.doc

21. Appendix I – Neuropathic Pain Symptom Inventory (NPSI)

NEUROPATHIC PAIN SYMPTOM INVENTORY (NPSI)

Correspondence: Dr Didier Bouhassira
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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.

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	

22. References

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Lexicon

CLINICAL STUDY PROTOCOL AMENDMENT 3
SUMMARY OF CHANGES

Protocol Number:	LX9211.1-202-PHN LX9211.202 (Abbreviated number)
Investigational Phase:	2
Protocol 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)
Amendment 3 Date:	15 October 2021
Amendment 2 Date:	03 March 2021
Amendment 1 Date:	23 October 2020
Original Version Date:	14 September 2020
Sponsor:	Lexicon Pharmaceuticals, Inc. 2245 Technology Forest Blvd, Level 11 The Woodlands, TX 77381-5261 Telephone: (281) 863-3000 Safety Data Facsimile: (832) 442-5462
[redacted]:	[redacted], MD [redacted] Lexicon Pharmaceuticals, Inc. Telephone: [redacted]

Rationale for Amendment

Protocol Amendment 3 includes the following changes to the protocol:

- Modification to plans for interim analysis and their implications
- The exclusion of patients with facial PHN are eligible for participation if trigeminal neuralgia has been excluded as a cause
- Change in the physical address of Lexicon Pharmaceuticals, Inc.

Attached is a detailed summary of each change included in this Amendment.

Page and/or Section	Text in Protocol Amendment 2	Text in Protocol Amendment 3	Rationale
Footers (Global)		Date Change	Editorial Change
pg. 1, 2	03 March 2021	15 October 2021	Administrative Change
pg. 1, 2	Lexicon Pharmaceuticals, Inc. 8800 Technology Forest Place The Woodlands, TX 77381-1160	Lexicon Pharmaceuticals, Inc. 2245 Technology Forest Blvd, Level 11 The Woodlands, TX 77381-5261	Administrative Change
pg. 8, 36 (Treatment Schema)	History of PHN ≥6 months from healing of rash	History of PHN ≥3 months from healing of rash	Global alignment of protocol
pg. 8	The interim analysis will also include formal statistical testing for efficacy, and should the prespecified stopping rule be met, the trial may stop after enrollment of the first 38 patients.	The interim analysis will allow for statistical testing of futility and should the prespecified futility boundary be crossed, and other data support a negative trial finding, consideration will be made to stop patient accrual.	Clarification
pg. 11, 41	Patient has PHN affecting the face (trigeminal nerve distribution)	Suspected or likely diagnosis of trigeminal neuralgia	Liberating facial PHN as exclusion if cause not related to trigeminal neuralgia
pg. 15 , 61	A proposed sample size of 74 randomized patients will yield 83.11% power to detect a true mean difference of -0.68 units between the LX9211 treatment group and placebo in the primary efficacy endpoint, assuming a common standard deviation of 1 unit and a 2-sided significance level of α=0.05.	A proposed sample size of 74 randomized patients will yield 82.27% power to detect a true mean difference of -0.68 units between the LX9211 treatment group and placebo in the primary efficacy endpoint, assuming a common standard deviation of 1 unit and a 2-sided significance level of α=0.05.	Clarification
Sec 3.6 Rationale for Study Design and Control Groups	The study is designed as a group sequential trial to accommodate the interim analysis, and to improve upon such a design, the interim analysis effect size result is used not only to possibly increase the sample size, but to aid in decisions of early stopping.	The study is designed as a group sequential trial to accommodate the interim analysis, and to improve upon such a design, the interim analysis effect size result is used not only to possibly increase the sample size, but to aid in decisions of early stopping for futility.	Clarification

Page and/or Section	Text in Protocol Amendment 2	Text in Protocol Amendment 3	Rationale
Sec 6.4.1 Termination of the Study Based on Planned Interim Analysis	The study may be terminated based on the conduct of a formal interim analysis of efficacy. Enrollment will not be temporarily halted while data for the interim analysis is being reviewed. The sample size may be increased based on the interim analysis. In the case that the statistical stopping rule for efficacy is not met, the study will continue through planned completion. This can be with the original proposed sample size of 74 patients or with an increased sample size, to a maximum of 148 patients. Details of these analyses are given in Section 10.4.5.7 of this protocol, and in the Statistical Analysis Plan (SAP) and Data Monitoring Committee (DMC) Charter documents. The interim analysis is planned as follows: Interim efficacy analysis using a 2-sided $\alpha = 0.05$ O'Brien-Fleming group sequential test. This analysis will occur when the first 38 patients have been accrued and followed to the endpoint at Week 6. The interim analysis of efficacy is to provide guidance for early stopping should the observed results be more favorable than originally expected. 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.	The study may be terminated based on the conduct of a formal interim analysis of futility. The interim analysis will be performed when the first 38 patients have been accrued and followed to endpoint at Week 6 or dropped out from the trial earlier, whichever event occurs first. Enrollment will not be temporarily halted while data for the interim analysis is being reviewed. The sample size may be increased based on the interim analysis. Details of the futility analysis are given in Section 10.4.5.7 of this protocol, and in the Statistical Analysis Plan (SAP) and Data Monitoring Committee (DMC) Charter documents. In addition to the planned interim analysis for futility, meetings for an independent DMC data reviews will be scheduled to ensure proper safety assessment during enrollment and study conduct.	Clarification
Section 6.7	The Sponsor's designee performing IXRS will not release the randomization schedule to any party except upon formal written request by the Sponsor at study end. The request must be approved by the appropriate Sponsor personnel, according to the Sponsor's standard operating procedures (SOPs). Details of any disclosure of the randomization schedule will be recorded in the	The Sponsor's designee performing IXRS will not release the randomization schedule to any party except upon formal written request by the Sponsor at study end. The request must be approved by the appropriate Sponsor personnel, according to the Sponsor's standard operating procedures (SOPs). Details of any disclosure of the randomization	Clarification

Page and/or Section	Text in Protocol Amendment 2	Text in Protocol Amendment 3	Rationale
	site's study files and the electronic Trial Master File (eTMF). A copy of the randomization schedule will also be sent to the Sponsor and/or designee. The blinding of the study will be broken after the database has been locked. To maintain continuous blinding and study integrity, analysis will be conducted by an independent statistician, and measures will be taken to ensure the validity of the data. To maintain continuous blinding and study integrity, analysis will be conducted by an independent statistician, and measures will be taken to ensure the validity of the data. Details of the unblinding process for the interim analysis will be detailed in the SAP and independent DMC Charter documents.	schedule will be recorded in the site's study files and the electronic Trial Master File (eTMF). A copy of the randomization schedule will also be sent to the Sponsor and/or designee. The blinding of the study will be broken after the database has been locked. To maintain continuous blinding and study integrity, analysis will be conducted by an independent statistician, and measures will be taken to ensure the validity of the data. To maintain continuous blinding and study integrity, analysis will be conducted by an independent statistician, and measures will be taken to ensure the validity of the data.	
Sec 10.1 Determination of Sample Size	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 (H0) and is unequal to 0 under the alternative hypothesis (H1); a 2-sided hypothesis under test. Under the H1, the difference in group means of LX9211 minus placebo is expected to be -0.8 units with a common standard deviation 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 standard deviation 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 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 (H0) and is unequal to 0 under the alternative hypothesis (H1); a 2-sided hypothesis under test. Under the H1, the difference in group means of LX9211 minus placebo is expected to be -0.8 units with a common standard deviation 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 standard deviation 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.	Clarification

Page and/or Section	Text in Protocol Amendment 2	Text in Protocol Amendment 3	Rationale
	the stated treatment difference under H1 with statistical power equal to 82.27% under a single stage design. The total planned N = 74 patients.	For a 2-sided test sized at α = 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.	
Sec 10.1 Determination of Sample Size	An O'Brien-Fleming upper boundary will be used to test for efficacy. The test for the upper boundary is 2-sided with α = 0.05. Based on these specifications a sample size of 74 patents is required for a 2-sided test with α = 0.05 and 83.11% power. Implementation of the interim analysis test slightly inflates the fixed sample, single stage design sample size estimate. A 1:1 randomization allocation ratio is planned for patient assignment to study treatment.	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.	Clarification
Sec 10.1 Sample Size Reestimation	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 83.11% (the original specified power).	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).	Clarification
Sec 10.4.5.7 Interim Analysis	An interim analysis of the primary endpoint will be performed to test for efficacy when approximately 50% of the planned information has been achieved.	An interim analysis of the primary endpoint will be performed to test for futility when approximately 50% of the planned information has been achieved.	Clarification

Page and/or Section	Text in Protocol Amendment 2	Text in Protocol Amendment 3	Rationale
Sec 10.4.5.7 Interim Analysis	An O'Brien-Fleming upper boundary will be used to test treatment group differences in the primary endpoint at 51.35% and 100% of the planned information. This particular group sequential test will be implemented by using the Lan-DeMets Type I error spending function. The monitoring boundary is constructed by assuming a 2-sided test with α= 0.05. The sequence of z-scores and respective nominal p-values at the 2 planned information times are 2.918 (p=0.004) and 1.970 (p=0.049). Assessment of other data available at the interim analysis will be used to aid the decision-making process (eg, secondary and other efficacy variables).	The patient number for the interim analysis has been rounded upward from 37 to 38 patients to yield the minimum number of patients nearest but greater than the 50% information fraction that preserves the 1:1 randomization ratio. A non-blinding 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).	Clarification
Various		Correction of typos, grammar, and punctuation throughout protocol	Administrative Change