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

NCT Number: NCT04455633

Document Date: Protocol Amendment 4: 09-September-2021

16.1.1 Protocol and Protocol Amendments

Clinical Study Protocol LX9211.1-201-DPN Amendment 4 (09 September 2021)

Clinical Study Protocol LX9211.1-201-DPN Amendment 3 (18 November 2020)

Clinical Study Protocol LX9211.1-201-DPN Amendment 2.0.1 – PK Substudy Sites Only (09 October 2020)

Clinical Study Protocol LX9211.1-201-DPN Amendment 2 (28 August 2020)

Clinical Protocol LX9211.1-201-DPN – Amendment 1 (17 March 2020)

Clinical Study Protocol LX9211-201-DPN (05 December 2019)

CLINICAL STUDY PROTOCOL AMENDMENT 4
SUMMARY OF CHANGES

Protocol Number:	LX9211.1-201-DPN LX9211.201 (Abbreviated number)
Investigational Phase:	2
Protocol Title:	A Phase 2, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of LX9211 in the Treatment of Diabetic Peripheral Neuropathic Pain (RELIEF-DPN 1)
Amendment 4 Date:	09 September 2021
Amendment 3 Date:	18 November 2020
Protocol Amendment 2.0.1 Date:	09 October 2020
Amendment 2 Date:	28 August 2020
Amendment 1 Date:	17 March 2020
Original Version Date:	05 December 2019
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] Clinical Development Lexicon Pharmaceuticals, Inc. Telephone: [redacted]

Rationale for Amendment

Protocol Amendment 4 includes the following changes to the protocol:

- Modification to plans for interim analyses and their implications
- Modification of the time window allowed for assessment of Orthostatic Vital Signs
- Increase to the number of study sites from 30 to 45
- Change in physical address of Lexicon Pharmaceuticals, Inc.
- Specified temporary dose interruptions are allowed based on tolerability issues at the Investigators consideration. Time limits to temporary dose interruptions have been included (no less than 3 days but no more than 5 days)
- Qualitative Patient Interview substudy will increase number of interviews to capture patients in the last part of the trial and look at the distribution

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

Page and/or Section	Text in Protocol Amendment 3	Text in Protocol Amendment 4	Rationale
Footers (Global)	18 November 2020	09 September 2021	Editorial Change
pg. 1, 2		Amendment 4 date provided	Administrative Change
pg. 1, 2	8800 Technology Forest Place The Woodlands, Tx 77381-1160	2245 Technology Forest Blvd, Level 11 The Woodlands, TX 77381-5261	Administrative Change
pg. 8	The interim analysis will occur when the first 141 patients have been accrued and followed to endpoint at Week 6.	The interim analysis will occur when the first 141 patients have been accrued and followed to endpoint at Week 6 or dropped out earlier, whichever time is sooner.	Clarification
pg. 8 Number of Patients	Up to 282 patients are expected to enroll in this study. An interim analysis will occur when the first 141 patients have been accrued and followed to endpoint at Week 6. The interim analysis will include formal statistical testing for efficacy, and should the prespecified stopping rule be met, the trial may stop after enrollment of the first 141 patients.	The proposed sample size is 282 patients, 94 randomized to each treatment group. The sample size will be reassessed at a planned interim analysis. The interim analysis will occur when the first 141 patients have been accrued and followed to endpoint at Week 6 or dropped out earlier, whichever time is sooner. Based on this assessment, the sample size will be reestimated and can remain as originally proposed or increased. The maximum increase is limited to 351 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. 8 Number of Study Sites	Approximately 30 sites in the US	Approximately 45 sites in the US	The number of sites has been increased to enhance recruitment due to experiencing a higher-than-expected Screen Failure rate

Page and/or Section	Text in Protocol Amendment 3	Text in Protocol Amendment 4	Rationale
pg. 13 Statistical Methods		The sample size can be increased to a maximum of 351 patients based on a reestimation procedure performed at the planned interim analysis.	Clarification
Sec 3.5- Rationale for Study Design and Control Groups		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 provide guidance in early stopping for futility. The option of sample size reestimation (SSR) allows the study to maintain statistical power at the original specified value, and guard against its reduction due to an unexpected increase in the dropout rate or variability associated with the primary endpoint measure.	Clarification
Sec 6- Study Population		The sample size may be increased to a maximum of 351 patients based on a planned interim analysis that allows for conduct of a sample size reestimation procedure.	Clarification
Sec 6- Study Population	A second substudy will enroll approximately 60 patients in a qualitative patient interview	A second substudy will enroll a minimum of 60 patients and not to exceed 85 patients to participate in a qualitative patient interview.	Qualitative Patient Interview substudy will increase number of interviews to capture patients in the last part of the trial and look at the distribution

Page and/or Section	Text in Protocol Amendment 3	Text in Protocol Amendment 4	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, which will evaluate efficacy. Enrollment will not be temporarily halted while data for the interim analysis is being reviewed. Details of the interim 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. The following statistical comparisons are planned for the 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 141 patients have been randomized and followed to the Week 6 visit, or dropped out earlier, whichever time is sooner. Enrollment will not be temporarily halted while data for the interim analysis is being reviewed. 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.	Clarification
Sec 6.4.1- Termination of the Study Based on Planned Interim Analysis	Interim efficacy analysis using a 2-sided overall $\alpha = 0.05$ O'Brien-Fleming group sequential test. This analysis will occur when the first 141 patients have been accrued and followed to the endpoint at Week 6. At each analysis, Dunnett's multiple comparison procedure will be used to control the overall Type I error rate for the 2 planned pairwise comparisons of each LX9211 group versus placebo. The interim analysis of efficacy is to provide guidance for early stopping should the observed results be more favorable than originally expected.	Noted text in Protocol Amendment 3 - Removed	Statistical Change

Page and/or Section	Text in Protocol Amendment 3	Text in Protocol Amendment 4	Rationale
Sec 6.4.1- Termination of the Study Based on Planned Interim Analysis	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	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
Sec 7.5- Dose Adjustment		In the case of tolerability issues, the investigator can consider a temporary dose interruption of no less than 3 days, but no more than 5 days. If adverse event continues once study drug has been reinitiated then patient's continued participation needs to be assessed.	Specified temporary dose interruptions are allowed based on tolerability issues at the Investigators consideration. Time limits to temporary dose interruptions have been included
Sec 9.4- Reporting of Serious Adverse Events and Pregnancies	Safety Hotline	Physician On-Call Hotline	Administrative Change
Sec 9.4- Reporting of Serious Adverse Events and Pregnancies	[redacted] MD Drug Safety Physician Email: [redacted] Phone: [redacted]	[redacted] MD Drug Safety Physician Email: [redacted] Phone: [redacted]	Safety Physician Contact Information - Administrative Change
Sec 9.4- Reporting of Serious Adverse Events and Pregnancies		[redacted] MD [redacted] Clinical Development Email: [redacted] Phone: [redacted]	Medical Monitor Contact Information added- Administrative Change
Sec 10.1- Determination of Sample Size		Proposed Samples Size	Editorial Change

Page and/or Section	Text in Protocol Amendment 3	Text in Protocol Amendment 4	Rationale
Sec 10.1- Determination of Sample Size		<u>Sample Size Reestimation</u> Due to the uncertainty in the outcome for the primary endpoint analysis secondary to potential variations in some of the key design parameters such as the dropout rate and standard deviation associated with the targeted treatment group difference, an unblinded SSR adaptation will be implemented at the time of the interim analysis testing for futility. This will occur when the first 141 patients have been accrued and followed thru Week 6 or dropped out early from the trial (whichever event happens first). Should a patient drop out early in the study, but return for the Week 6 visit, the Week 6 data will be used in the analysis. The Chen-DeMets-Lan method will be used for the unblinded SSR since it requires minimal change from a group sequential test. This method requires specification for a number of criteria related to the allowable conditions for increasing the sample size that ensures that ordinary group sequential methods can be applied while seeing that the overall error is not inflated compared to the original group sequential design. The 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 80.3% (the original	Implemented Parameters at time of the efficacy interim analysis have been provided.

Page and/or Section	Text in Protocol Amendment 3	Text in Protocol Amendment 4	Rationale
		specified power under the group sequential design). The SSR is linked to the projected effect size falling within this "promising" or "favorable" range of conditional power. Having satisfied these 2 main conditions, the Type I error rate after increasing the sample size until the conditional power equals the original target power will not be greater than the Type I error from the originally proposed design. To derive the reestimated number of patients at the interim analysis, a simulation will be made that inputs: the observed group mean difference and its common standard deviation, a value for the maximum total number of patients (E[Max]) equal to 351 patients and, specification that the reestimation rule is the Exact E method. The Exact E method increases the patient number total until the desired conditional power is achieved.	
Sec 10.4.1.1 – Extent of study drug exposure	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 treatment exposure will be the total number of days of administration of the study drug.	Clarification to duration of treatment exposure

Page and/or Section	Text in Protocol Amendment 3	Text in Protocol Amendment 4	Rationale
Sec 10.4.5.7- Interim Analyses	An O'Brien-Fleming upper boundary will be used to test treatment group differences in the primary endpoint at 50% 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 an overall $\alpha = 0.05$. The sequence of z-scores and respective nominal p-values at the 2 planned information times for each pairwise comparison is 3.281 (p=0.001) and 2.199 (p=0.028). Assessment of other data available at the interim analysis will be used to aid the decision-making process (eg, secondary and other efficacy variables).	A non-blinding futility boundary will be used to test treatment group differences in the primary endpoint at 50% of the original planned information. The set of boundary values will be derived by using a beta spending function and specification of a power family with value = 3.672. The monitoring boundary is constructed by assuming a 1-sided test with a per comparison Type I error rate = 0.0141, assuring an overall $\alpha = 0.025$ (or a two-sided $\alpha = 0.05$) for the two LX9211 versus placebo comparisons. Use of this beta spending function for futility testing is conservative and results in cumulative beta error rates of 0.015 and 0.197 at the interim and final analyses, respectively. Application of the futility analysis is to serve as a guideline and is not the only source of information used to evaluate the trial for a negative finding. Assessment of other data available at the interim analysis will be used to qualify the trial for a recommendation of futility (eg, secondary and other efficacy variables, safety data).	Interim Analyses- Statistical Update
Sec 13- Appendix A- Schedule of Events (footer)	d. Orthostatic vitals will be collected on the Day 1 Visit 2 hours post dose of double-blind study drug.	d. Orthostatic vitals will be collected on the Day 1 Visit 2 hours (± 10 min.) post dose of double-blind study drug.	Time window added to aid in timely collection of Orthostatic Vitals at the study sites

CLINICAL STUDY PROTOCOL

Protocol Number:	LX9211.1-201-DPN LX9211.201 (Abbreviated number)
Investigational Phase:	Phase 2
Protocol Title:	A Phase 2, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of LX9211 in the Treatment of Diabetic Peripheral Neuropathic Pain (RELIEF-DPN 1)
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Original Version Date:	05 December 2019
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] Clinical Development Lexicon Pharmaceuticals, Inc. Telephone: [redacted]

Investigator Signature Page

Protocol Number:	LX9211.1-201-DPN
Protocol Title:	A Phase 2, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of LX9211 in the Treatment of Diabetic Peripheral Neuropathic Pain (RELIEF-DPN 1)
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Sponsor:	Lexicon Pharmaceuticals, Inc. 2245 Technology Forest Blvd, Level 11 The Woodlands, TX 77381-5261 Telephone: (281) 863-3000

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) [redacted]	[redacted]
[redacted] (Signature)	Date
[redacted] MD	
[redacted] (Printed Name)	

1. Synopsis

Name of Study Drug	LX9211 phosphate
Protocol Number	LX9211.1-201-DPN LX9211.201 (Abbreviated number)
Protocol Title	A Phase 2, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of LX9211 in the Treatment of Diabetic Peripheral Neuropathic Pain (RELIEF-DPN 1)
Primary Objective	To evaluate the efficacy of LX9211 in reducing pain related to diabetic peripheral neuropathy (DPN)
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 Brief Pain Inventory - DPN (BPI-DPN), the 11-point 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 following the 6-week double-blind Treatment Period
Secondary Efficacy Endpoints	• Proportion of patients with ≥30% reduction in pain intensity in ADPS based on Question 5 of the Brief Pain Inventory - DPN (BPI-DPN) from Baseline to Week 6 • Proportion of patients with ≥50% reduction in pain intensity in ADPS based on Question 5 of the Brief Pain Inventory - DPN (BPI-DPN) from Baseline to Week 6 • Change from Baseline to Week 6 in the severity of pain and interference of pain with sleep and other aspects of the patient's life based on the Brief Pain Inventory (BPI) Short Form for diabetic peripheral neuropathy (BPI-DPN) • Proportion of patients discontinuing treatment due to lack of efficacy defined as increase in ADPS based on Question 5 of the Brief Pain Inventory - DPN (BPI-DPN) from Baseline of 30% • Patient Global Impression of Change (PGIC) at Week 6 • Time to loss of efficacy from Week 6 to Week 11 among patients achieving at least 30% reduction in pain intensity in ADPS based on Question 5 of the Brief Pain Inventory - DPN (BPI-DPN) at Week 6
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 BPI-DPN

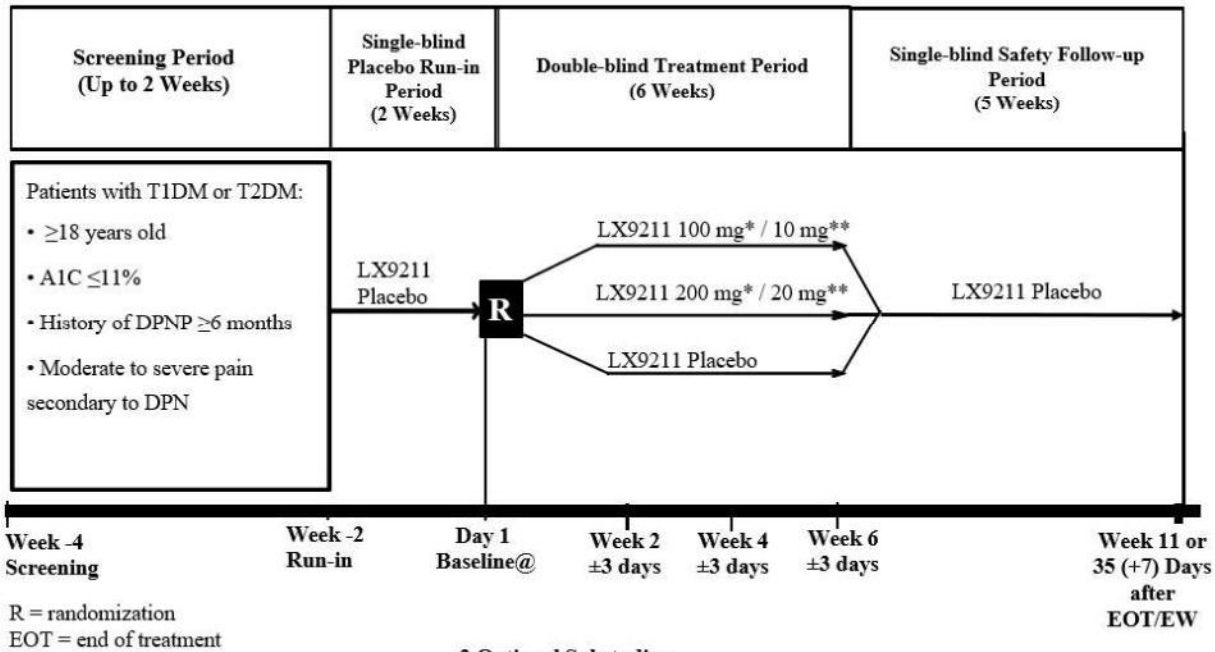
	• Proportion of patients with ≥30% reduction from Baseline in ADPS, based on Question 5 of the BPI-DPN by week • Proportion of patients with ≥50% reduction from Baseline in ADPS, based on Question 5 of the BPI-DPN by week • Cumulative distribution function of percent change in ADPS based on Question 5 of the BPI-DPN from Baseline to Week 6 comparing each LX9211 treatment group to placebo • Cumulative distribution function of percent change in ADPS based on Question 5 of the BPI-DPN from Week 6 to Week 11 comparing each LX9211 treatment group to placebo
Pharmacokinetic (PK) Objectives	To evaluate plasma C_{trough} levels of LX9211 at 2 oral dose levels in patients with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) with chronic diabetic peripheral neuropathic pain (DPNP) over a 6-week period The full pharmacokinetic (PK) profile of LX9211 will be evaluated in an optional substudy conducted in patients who consent to intensive PK sampling over the course of the treatment period.
Safety 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 DPNP. 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 at Week 11 (at the conclusion of the Safety Follow-up Period). Male and female patients of nonchildbearing potential ages 18 years and older, diagnosed with T1DM or T2DM, an A1C ≤11%, with chronic DPNP, and who meet all inclusion and no exclusion criteria are eligible for enrollment. Eligible patients may continue use of medications prescribed for DPNP including pregabalin, gabapentin, and antidepressant medications, as long as they have been at stable doses for at least 1 month prior to screening. Use of any opioid medications for the management of DPNP within the 2 months prior to Screening is not permitted.

	Screening Period: After signing the Informed Consent Form (ICF), all patients will enter a Screening Period of up to 2 weeks. Following confirmation of eligibility criteria, patients will enter the following study periods: **Run-in Period:** After meeting Screening eligibility criteria, patients will enter a 2-week single-blind Run-in Period. On day 1 of the Run-in Period patients will be 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 the intensity of their DPNP over the previous 24 hours based on Question 5 of the BPI-DPN by answering the question "Please rate your pain due to your diabetes by indicating the one number that best describes your pain on the average." (0 [no pain] to 10 [pain as bad as you can imagine]) in their daily pain diary and will rate the interference of pain with sleep by completing Question 9F of the BPI-DPN. The ADPS will be calculated using all available daily pain diary data. This derived value of the ADPS 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 may be rescreened ONCE after discussion with the Medical Monitor. Patients who begin the Screening period prior to this amendment and who otherwise would qualify for the study may be rescreened again so as to allow them to begin the Run-in Phase following implementation of this amendment. **Randomization/Double blind Treatment Period**: Patients who successfully complete the 2-week single-blind placebo Run-in Period and meet all other eligibility criteria will enter a 6-week double-blind Treatment Period. Patients will be randomly assigned in a 1:1:1 ratio among the following 3 treatment groups: • **Group 1:** LX9211 100 mg* / 10 mg**, once daily (qd) • **Group 2:** LX9211 200 mg* / 20 mg**, qd • **Group 3:** Placebo, qd * Loading dose (Day 1)

	** Maintenance dose (Day 2 – Week 6 Visit) Implementation of the treatment randomization schedule will be centralized. A 1:1:1 ratio for assigning patients among the treatment groups will be accomplished by use of randomly permuted blocks of fixed size. On Day 1, patients will receive 1 of 2 dose levels of LX9211 or placebo, based on their treatment assignment, to be given as a loading dose at the clinic. 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 patients will rate and record the intensity of their DPNP over the previous 24 hours based on Question 5 of the BPI-DPN by answering the question "Please rate your pain due to your diabetes by indicating the one number that best describes your pain on the average." (0 [no pain] to 10 [pain as bad as you can imagine]), will record the use of rescue medication (acetaminophen), and will rate the interference of pain with sleep by completing Question 9F of the BPI-DPN. The ADPS will be calculated using all available data, however, a minimum of 4 days (consecutive or nonconsecutive) from the last week prior to each clinic visit is required for the calculation of weekly averages. If a patient is unable to tolerate their DPNP, they are encouraged to discuss treatment options with the Investigator. At the Investigator's direction, the patient may be permitted to take acetaminophen (up to a maximum of 3 grams per day) as a rescue medication. If rescue medication does not provide adequate pain relief, the patient may discontinue from further participation in the study after consultation with the Investigator. Patients 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 every morning taken at home. Each evening patients will rate and record the intensity of their DPNP over the previous 24 hours based on Question 5 of the BPI-DPN by answering the question "Please rate your pain due to your diabetes by indicating the one number that best describes your pain on the average." (0 [no pain] to 10 [pain as bad as you can imagine]), will record the use of rescue medication (acetaminophen), and will rate the interference of pain with sleep by completing Question 9F of the BPI-DPN.

	Blood samples for the determination of plasma LX9211 trough levels (C_{trough}) will be drawn predose on Day 1 and at Weeks 2, 4, and 6, just prior to the dosing of study drug on the day of the clinic visit. At the Week11 EOT/EW Visit a final sample will be collected. During the Screening Visit, patients may choose to participate in 1 or both of the 2 optional substudies. The PK substudy will include approximately 30 patients. These patients will be confined to a clinical research unit (CRU) twice during the study for intensive PK evaluation and biomarker evaluation: prior to and following the first dose of study drug and prior to and following their final dose of study drug (planned for Week 6). The second optional substudy is a qualitative patient interview following the Week 6 visit (or after early study withdrawal), which will include approximately 60 patients. The telephone interview is designed to gain insight and understanding of patients' experiences with symptoms of DPNP and to assess relevance and clinical meaningfulness of symptom improvements (eg, reduction in pain) with LX9211 treatment. The study design is presented in the diagram below:

Treatment Schema:



R = randomization
EOT = end of treatment
EW = early withdrawal

*- 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

2 Optional Substudies:

- **PK Evaluation and possible biomarker analysis (up to 30 patients)** – Days 1 and 2, Week 2, Week 4, Week 6 or EOT/EW, Week 11 or 35 Days after EOT/EW
- **Exit Phone Interview** – Within 2 to 3 weeks following the Week 6 Visit or EOT/EW

Number of Patients	The proposed sample size is 282 patients, 94 randomized to each treatment group. The sample size will be reassessed at a planned interim analysis. The interim analysis will occur when the first 141 patients have been accrued and followed to endpoint at Week 6 or dropped out earlier, whichever time is sooner. Based on this assessment, the sample size will be reestimated and can remain as originally proposed or increased. The maximum increase is limited to 351 patients. The interim analysis will allow for statistical testing of futility and should the prespecified futility boundary be crossed, and other data

<table>
<tr><td></td><td>support a negative trial finding, consideration will be made to stop patient accrual.

A subset of approximately 30 patients will be recruited to participate in the PK and possible biomarker analyses substudy.

Approximately 60 patients will be recruited to participate in a qualitative patient interview.</td></tr>
<tr><td>Study Population</td><td>Male and female patients who are ≥18 years of age at the time of Screening will be enrolled. Patients will have a diagnosis of T1DM or T2DM with A1C ≤11% and a history of ≥6 months of chronic DPNP that meets pain criteria at the end of the Run-in Period.</td></tr>
<tr><td>Number of Study Sites</td><td>Approximately 45 sites in US</td></tr>
<tr><td>Treatments</td><td>Each patient will be randomized to 1 of the following groups:
<table>
<tr><th>Treatment Group</th><th>Loading Dose (Day 1)</th><th>Maintenance Dose (Day 2 to Week 6 / EOT/EW)</th></tr>
<tr><td>Group 1:
LX9211 100 mg*/10 mg**</td><td>2 x 50-mg LX9211 tablets
+
2 x Placebo tablets</td><td>1 x 10-mg LX9211 tablet, qd</td></tr>
<tr><td>Group 2:
LX9211 200 mg*/20 mg**</td><td>2 x 50-mg LX9211 tablets
+
2 x 50-mg LX9211 Tablets</td><td>1 x 20-mg LX9211 tablet, qd</td></tr>
<tr><td>Group 3:
Placebo</td><td>2 x Placebo tablets
+
2 x Placebo tablets</td><td>1 x Placebo tablet, qd</td></tr>
</table></td></tr>
<tr><td>Route of Administration</td><td>Oral</td></tr>
<tr><td>Duration of Treatment</td><td>Patients will be treated with placebo or active study drug for 13 weeks (2 weeks of single-blind placebo, 6 weeks of double-blind placebo or LX9211, and 5 weeks of single-blind placebo). Patient participation will be approximately 105 days (assuming no rescreening), 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.</td></tr>
<tr><td>Inclusion Criteria</td><td>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:</td></tr>
</table>

	1. Patient has given written informed consent to participate in the study in accordance with local regulations 2. Adult male and 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. Body mass index ≥18.0 to ≤40.0 kg/m^2 at Screening 4. Diagnosis of T1DM or T2DM with chronic DPNP, (defined as distal symmetric polyneuropathy characterized by burning pain, paresthesia's, and numbness with reduced or absent deep tendon reflex at both ankles) at Screening 5. Michigan Neuropathy Screening Instrument (MNSI) Part B score of ≥2.5 at Screening based on Items 1-4 6. Pain from DPN present for at least 6 months 7. At the Screening Visit, A1C must be ≤11%. 8. Stable regimen for the treatment of T1DM or T2DM for ≥1 month prior to Screening, consisting of diet and/or oral or injectable antidiabetic therapy. **Note:** Modifications in insulin dose are permitted for patients using insulin. 9. Moderate to severe pain as confirmed by average pain score based on Question 5 of the BPI-DPN recorded in the pain diary in the 14 days prior to randomization (Run-in Period) 10. 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

	11. 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 DPNP: a. Patients should not have any other neurological disorder or conditions that can cause symptoms that may mimic peripheral neuropathy or that might confound assessment of distal symmetrical sensory polyneuropathy, and especially should not have any neuropathy due to nondiabetic causes. Patients with any condition that mimics peripheral neuropathy such as: stroke with distal neurological deficit; amyotrophy; polyradiculopathy; history of transient ischemic attacks; multiple sclerosis; mononeuropathy multiplex should be excluded. b. Other causes of diffuse painful peripheral neuropathy such as: paraproteinemia, untreated hypothyroidism (previously treated hypothyroidism not excluded if treated and euthyroid for at least 6 months), vitamin B12 deficiency, neurologically-evident vasculitis, malignancy, amyloidosis, renal insufficiency, connective tissue disease (eg, Sjogren's, systemic lupus erythematosus), porphyria, hereditary motor sensory neuropathy, postherpetic neuralgia, 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. Patients 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. History of neurolytic or neurosurgical therapy for DPNP 5. Use of opioid medications for management of DPNP within the 2 months prior to the Screening Visit. **Note:** Brief use (<1 week) of opioid medication for management of non-DPNP acute pain (eg, tooth extraction/acute injury) at least 1 month prior to Screening Visit is permitted. 6. Use of NSAIDs less than 2 weeks prior to the Screening Visit 7. A positive urine drug test for drugs of abuse and cannabinoids. **Note:** Cannabidiol, if used for mood or sleep, is acceptable. If used for DPNP, it would be allowed if it is the only concomitant medication being taken for DPNP. If it is not the only medication being taken for DPNP, it should be withdrawn at least 1 month prior to Screening. 8. Patients with 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. 9. Patients with abnormal kidney function test (glomerular filtration rate [GFR] <60 mL/min as calculated using the Cockcroft-Gault equation) at Screening or renal dysfunction requiring hemodialysis 10. Patients with a history of epilepsy or seizure disorder requiring treatment with antiepileptic drugs 11. Presence of clinically significant physical examination (PE) findings other than DPNP, 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 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) 12. Receipt of any investigational agent or study drug within 30 days or 5 half-lives, whichever is longer, prior to Screening 13. 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:** Prophylactic vaccines, such as influenza, pneumococcal, or TDAP vaccine will be allowed if administered >7 days prior to randomization. 14. Prior exposure to LX9211 15. 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 16. Presence of any skin condition such as ulcers, lower extremity amputations, etc., which interferes with assessment of DPNP 17. Existence of any surgical 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 (eg, bariatric surgery) 18. History of any major surgery within 3 months prior to Baseline or surgery that is anticipated to be performed during the study period 19. History of any active infection within 30 days prior to Baseline, if deemed clinically significant by the Investigator, Medical Monitor, and/or the Sponsor 20. 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. 21. Donation or loss of >500 mL of blood or blood product within 3 months prior to Baseline 22. Inability or difficulty swallowing whole tablets 23. 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 24. 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 25. Patients who refuse to participate in processes established by the Sponsor, to minimize duplicate patients 26. 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
Statistical Methods	A sample size of 75 patients per treatment group who complete the 6-week Double-blind Treatment Period will yield 80% power to detect a true mean difference of 1 unit between at least 1 LX9211 treatment group and placebo in ADPS change from Baseline to Week 6, assuming a common standard deviation of 2 and an overall significance level of α=0.05 (2-sided Dunnett's test). Accounting for a uniform dropout rate of 20%, a total of 282 patients (94 patients per treatment group) will be enrolled and randomly assigned to treatment in a 1:1:1 ratio. This sample size is adjusted for the multiple comparisons of each LX9211 treatment group with placebo (Westfall, 1999). The sample size can be increased to a maximum of 351 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 at least 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: BPI-DPN score and NPSI score, measured at multiple time points, a similar modeling strategy used for the primary endpoint will be applied. PGIC and the proportion of responders based on Question 5 of the BPI-DPN, 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.
Pharmacokinetic Substudy Assessments	The Pharmacokinetic (PK) Population for the PK Substudy patients who receive a dose of study drug and who have a predose sample and at least the minimum number of samples required to estimate the PK parameters. For the PK substudy (approximately 30 patients), patients will be admitted to the CRU either the day before the first dose (Day -1) or prior to the first dose of study drug (Day 1). Blood samples will be collected at the following time points: • Day 1: predose (0 hr), and 0.5, 1, 2, 4, 6, 8, 10, 12, 14, and 16 hours postdose; • Day 2: predose (24 hrs post Day 1 dose)

	Patients will be discharged following the predose sample collection and administration of the Day 2 dose. Patients will be admitted to the study facility for intensive sampling again on the day prior to the Week 6 visit or prior to dosing at the Week 6 visit. Blood samples will be collected at the following time points: • Week 6: predose (0 hr), 0.5, 1, 2, 4, 6, 8, 10, 12, 14, and 16 hours postdose, 24 hours after Week 6 Dose Patients will be discharged following the 24-hour postdose sample collection. Patients participating in the PK substudy will also have C_{trough} blood samples drawn predose on Day 1 and at Weeks 2, 4, and 6, just prior to the dosing of study drug on the day of the clinic visit. At the Week 11/EOT/EW Safety Follow-up Visit, a final sample will be collected.
Pharmacokinetic Substudy Analysis	If quantifiable plasma concentrations are available, the PK parameters will be derived using non-compartmental techniques PK parameters will include, but are not limited to: maximum plasma concentrations (C_{max}), C_{max} at steady-state (C_{ss}), time to maximum plasma concentration (t_{max}), trough plasma concentration (C_{trough}), area under the concentration-time curve from time 0 to 24 hours (AUC_{0-24}), AUC from 0 to the last quantifiable concentration ($AUC_{0-tlast}$), apparent terminal elimination half-life (t1/2), apparent terminal elimination rate constant (λz), apparent volume of distribution (Vz/F), apparent total body clearance (CL/F), and weight-adjusted clearance (CL/F/kg). Arithmetic means; coefficients of variation (%CV); standard deviations (SD); median, minimum, and maximum values; and number of observations will be calculated for PK parameters separately. Plasma concentrations and time deviation data will be presented in the data listings by treatment, patient, and nominal time point, and plasma concentration data will be summarized descriptively by dose and nominal time point. Individual and mean plasma concentration versus nominal time profiles will be displayed graphically on linear-linear scales. Individual and dose normalized C_{trough} values will be summarized by treatment group using descriptive statistics. Data listings of all PK parameters will be provided.
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 dose level) 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 in 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
A1C	hemoglobin A_{1c} / glycosylated hemoglobin (previously $HbA1_c$)
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
BPI	Brief Pain Inventory
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence intervals
CMP	comprehensive metabolic panel
CRO	contract research organization
DPN	diabetic peripheral neuropathy
DPNP	diabetic peripheral neuropathic pain
eCRF	electronic Case Report Form
ECG	electrocardiogram
EMG	electromyogram
EOT	end of treatment
ERC	Ethics Review Committee
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

Abbreviation	Definition
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
MedDRA	Medical Dictionary for Regulatory Activities
MNSI	Michigan Neuropathy Screening Instrument
NFR	nociceptive flexion reflex
NOAEL	no observable adverse effect level
PBMC	peripheral blood monocytes
PD	pharmacodynamic
PE	physical examination
PK	pharmacokinetic(s)
PHN	postherpetic neuralgia
PRO	patient reported outcome
RBC	red blood cells
SAE	serious adverse event
SOP	standard operating procedure
SD	standard deviation
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
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

Definitions of Pharmacokinetic Terms

Parameter	Definition
AUC	Area under the concentration-time curve
$AUC_{0\text{-}24}$	area under the concentration-time curve from time 0 to 24 hours
$AUC_{0\text{-}tlast}$	area under the concentration-time curve from time 0 to time t_{last}, where t_{last} is the last time point with a measurable concentration
$AUC_{0-\infty}$	area under the concentration-time curve from time 0 to infinity
C_{max}	maximum plasma concentration
C_{trough}	trough plasma concentrations
C_{ss}	plasma concentration at steady state
t_{max}	time to maximum plasma concentration
$t_{1/2}$	apparent terminal elimination half-life
λ_z	apparent terminal phase elimination rate constant
Vz/F	apparent volume of distribution
CL/F	apparent total body clearance
CL/F/kg	weight adjusted clearance

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 2 neuropathic pain models in rats (CCI and STZ 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. 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.

3.2.5 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. In embryo-fetal development studies, the NOAEL for LX9211 phosphate was determined to be 10 mg/kg/day in the rat and 4 mg/kg/day in the rabbit.

Additional details can be found in the IB.

3.2.6 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 3630 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 1370 ng/mL for males and females, respectively (mean of 1090 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 high dose in the current DPN study.

3.2.7 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 1860 and 1090 ng*hr/mL, respectively (mean 1470 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 et al, 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).

3.2.8 Embryo-Fetal Development Study in Rats

In the rat embryo-fetal development study, doses of LC9211 phosphate 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.

3.2.9 Embryo-Fetal Development Study in Rabbits

In the rabbit embryo-fetal development study, 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 AUC0-24 were 261 ng/mL and 4200 ng*hr/mL, respectively, for LX9211.

3.3 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 (IV) Administration in Healthy Male Subjects. A cohort of 6 male subjects were exposed to a single oral dose of ^{14}C-LX9211 (nominal 50 mg free drug). Drug-related material in urine and feces was recovered for up to 34 days. The mean recovery percentage of drug-related material was 77.9%, with 48.7% collected in urine and 29.2% being collected 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 addition, a separate cohort of 6 subjects underwent an evaluation to establish the absolute oral bioavailability of LX9211. A single oral dose of 50 mg was administered, followed by an IV microdose (^{14}C-9211 50 μg). 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.

Both 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 randomized to receive LX9211.

The results from the LX9211-101 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 of 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 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. 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,

3.4 Rationale for Current Study

3.4.1 Rationale for Selection of Dose

The doses of LX9211 selected for evaluation in the current study were 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 levels selected in this study, 100 mg and 200 mg loading doses followed by 10 mg and 20 mg maintenance doses, respectively, are expected to be well tolerated and represent an adequate range for dose exploration.

3.5 Rationale for Study Design and Control Groups

The randomized, placebo-controlled, double-blind clinical design allows for unbiased comparison of efficacy and safety between 2 different dose levels of 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 doses of 100 mg and 200 mg, which were 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 provide guidance in early stopping for futility. The option of sample size reestimation (SSR) allows the study to maintain statistical power at the original specified value, and guard against its reduction due to an unexpected increase in the dropout rate or variability associated with the primary endpoint measure.

4. Study Objectives

4.1 Primary Objective

- To evaluate the efficacy of LX9211 in reducing pain related to diabetic peripheral neuropathy (DPN)

4.2 Secondary Objective(s)

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

4.3 Other Objective(s)

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

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

Safety will be assessed by AEs, vital signs, ECG findings, and laboratory parameters.

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 DPNP.

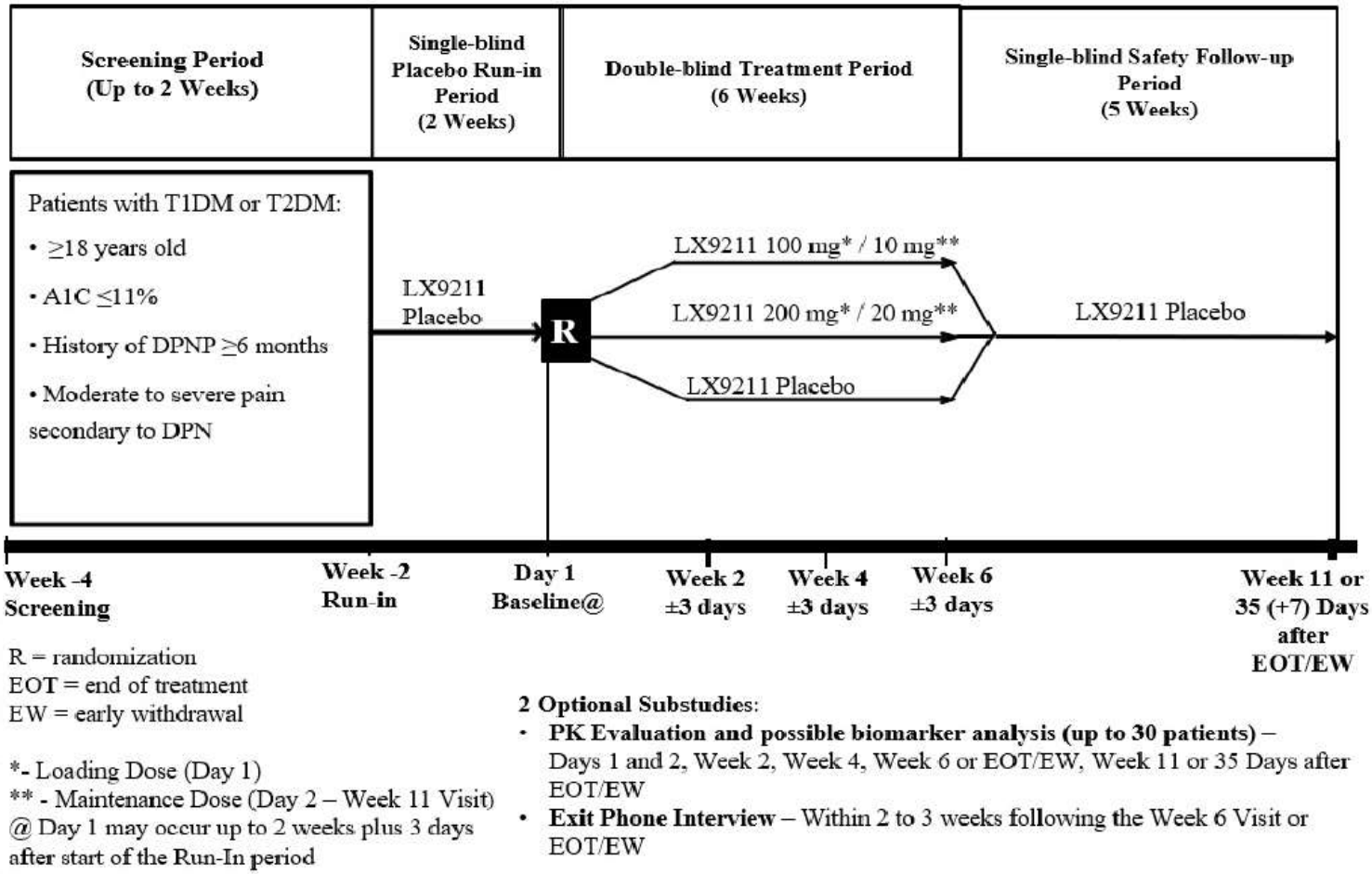
Scheduled study visits in the clinic will occur during Screening; at the initiation of the 2-week single-blind placebo Run-in Period; on Day 1 (Baseline) and during Weeks 2, 4, and 6 of the double-blind Treatment Period, and at Week 11 (Week 5 of the single-blind Safety Follow-up Period).

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

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

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

*- 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

2 Optional Substudies:

- **PK Evaluation and possible biomarker analysis (up to 30 patients)** – Days 1 and 2, Week 2, Week 4, Week 6 or EOT/EW, Week 11 or 35 Days after EOT/EW
- **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. Following confirmation of eligibility criteria, patients will enter the Run-in Period. **Note:** Patients who fail Screening may be rescreened ONCE after discussion with the Medical Monitor. Patients who begin the Screening Period prior to this amendment and who otherwise would qualify for the study may be rescreened again so as to allow them to begin the Run-in Phase following implementation of this amendment.

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 in the morning. Each evening patients will rate and record the intensity of their DPNP over the previous 24 hours based on Question 5 of the BPI-DPN by answering the question "Please rate your pain due to your diabetes by indicating the one number that best describes your pain on the average." (0 [no pain] to 10 [pain as bad as you can imagine]) in their daily pain diary and will rate the interference of pain with sleep by completing Question 9F of the BPI-DPN. The ADPS will be calculated using all available daily pain diary data. In order to qualify for randomization, patients must have completed ≥70% of the daily pain diary entries during the week prior to randomization, meet criteria for moderate to severe pain, and demonstrate ≥80% compliance with taking the expected amount of placebo tablets during the Run-in Period. During the Run-in Period patients will not be allowed to use any rescue medication. On the morning of the Run-in Visit, patients may consume a light meal prior to the visit.

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

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 1:1:1 ratio among the following 3 treatment groups:

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

- **Group 3:** Placebo, qd

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

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

On Day 1, patients will be assigned to 1 of 2 dose levels of LX9211 or placebo, based on their treatment assignment, to be given as a loading dose at the clinic. Patients will remain at the clinic for observation for 2 hours following dosing. At 2 hours, orthostatic vital signs will be obtained (heart rate and blood pressure) after which time patients may be released.

The loading dose will be followed by a daily maintenance dose taken at home 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 patients will rate and record the intensity of their DPNP over the previous 24 hours based on Question 5 of the BPI-DPN by answering the question "Please rate your pain due to your diabetes by indicating the one number that best describes your pain on the average." (0 [no pain] to 10 [pain as bad as you can imagine]), record the use of rescue medication (acetaminophen), and rate the interference of the patient's pain with sleep based on Question 9F of the DPI-PHN. 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 of weekly averages.

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

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

Patients discontinuing the study prior to completion of the Week 6 Visit should also complete the Safety Follow-up Visit 5 weeks later.

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 and take 1 tablet of single-blind study drug each morning during this period.

During the 5-week single-blind Safety Follow-up Period, patients are allowed use of rescue medication (acetaminophen) if needed.

5.1.5 Optional Substudies

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

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

and following the first dose of study drug and prior to and following their final dose of study drug (planned for Week 6).

The second optional substudy, a qualitative patient interview, will include approximately 60 patients. The telephone interview will be designed to gain insight and understanding of patients' experiences with symptoms of DPNP and to assess relevance and clinical meaningfulness of symptom improvements (eg, reduction in pain) with LX9211 treatment.

6. Study Population

Up to 282 patients (94/treatment group) are expected to enroll in this study in order to complete 225 (75/treatment group). The sample size may be increased to a maximum of 351 patients based on a planned interim analysis that allows for conduct of a sample size reestimation procedure.

A subset of approximately 30 patients will be recruited to participate in the PK and biomarker analyses optional substudy.

A second substudy will enroll a minimum of 60 patients and not to exceed 85 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 and 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. Body mass index ≥18.0 to ≤40.0 kg/m^2 at Screening
4. Diagnosis of T1DM or T2DM with chronic DPNP, (defined as distal symmetric polyneuropathy characterized by burning pain, paresthesias, and numbness with reduced or absent deep tendon reflex at both ankles) at Screening
5. Michigan Neuropathy Screening Instrument (MNSI) Part B score of ≥2.5 at Screening based on Items 1-4
6. Pain from DPN present for at least 6 months
7. At the Screening Visit, A1C must be ≤11%.
8. Stable regimen for the treatment of T1DM or T2DM for ≥1 month prior to Screening, consisting of diet and/or oral or injectable antidiabetic therapy. **Note:** Modifications in insulin dose are permitted for patients using insulin.
9. Moderate to severe pain as confirmed by average pain score based on Question 5 of the BPI-DPN recorded in the pain diary in the 14 days prior to randomization (Run-in Period)
10. 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
11. 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 DPNP:

    a. Patients should not have any other neurological disorder or conditions that can cause symptoms that may mimic peripheral neuropathy or that might confound assessment of distal symmetrical sensory polyneuropathy, and especially should not have any neuropathy due to nondiabetic causes. Patients with any condition that mimic peripheral neuropathy such as stroke with distal neurological deficit; amyotrophy; polyradiculopathy; history of transient ischemic attacks; multiple sclerosis; mononeuropathy should be excluded.

    b. Other causes of diffuse painful peripheral neuropathy such as: paraproteinemia, untreated hypothyroidism (previously treated hypothyroidism not excluded if treated and euthyroid for at least 6 months), vitamin B12 deficiency, neurologically-evident vasculitis, malignancy, amyloidosis, renal insufficiency, connective tissue disease (eg, Sjogren's, systemic lupus erythematosus), porphyria, hereditary motor sensory neuropathy, postherpetic neuralgia, 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. Patients 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 criteria (DSM-5) 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. History of neurolytic or neurosurgical therapy for DPNP
5. Use of opioid medications for management of DPNP within the 2 months prior to the Screening Visit **Note:** Brief use (<1 week) of opioid medication for management of non-DPNP acute pain (eg, tooth extraction/ acute injury) at least 1 month prior to screening is permitted.
6. Use of chronic NSAIDs less than 2 weeks prior to the Screening Visit.
7. A positive urine drug test for drugs of abuse and cannabinoids. **Note:** Cannabidiol, if used for mood or sleep, is acceptable. If used for DPNP it would be allowed if it is the only concomitant medication being taken for DPNP. If it is not the only medication being taken for DPNP, it should be withdrawn at least 1 month prior to Screening
8. Patients with 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.
9. Patients with significant abnormal kidney function test (glomerular filtration rate [GFR] <60 mL/min as calculated using the Cockcroft-Gault equation) at Screening or renal dysfunction requiring hemodialysis
10. Patients with epilepsy or seizure disorder requiring treatment with antiepileptic drugs
11. Presence of clinically significant physical examination (PE) findings other than DPNP, 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 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 (Martin, 1994) or structural heart disease)

12. Receipt of any investigational agent or study drug within 30 days or 5 half-lives, whichever is longer, prior to Screening
13. 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:** Prophylactic vaccines, such as influenza, pneumococcal, or TDAP vaccine will be allowed if administered >7 days prior to randomization.
14. Prior exposure to LX9211
15. 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
16. Presence of any skin condition such as ulcers, lower extremity amputations, etc., which interferes with assessment of DPNP
17. Existence of any surgical 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 (eg, bariatric surgery)
18. History of any major surgery within 3 months prior to Baseline or surgery that is anticipated to be performed during the study period
19. History of any active infection within 30 days prior to Baseline, if deemed clinically significant by the Investigator, Medical Monitor, and/or the Sponsor
20. 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.
21. Donation or loss of >500 mL of blood or blood product within 3 months prior to Baseline
22. Inability or difficulty swallowing whole tablets
23. 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
24. 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
25. Patients who refuse to participate in processes established by the Sponsor, to minimize duplicate patients
26. 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

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

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

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 141 patients have been randomized and followed to the Week 6 visit, or dropped out earlier, whichever time is sooner. Enrollment will not be temporarily halted while data for the interim analysis is being reviewed. 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 meet every 2 months, plus at the time of 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 among 3 parallel treatment groups in a 1:1:1 manner. A randomization schedule will be centralized and stratified by the ADPS during the Run-in period based on moderate or severe pain. The randomization schedule will also account for the optional PK and biomarkers substudy. 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-blinded study, the designated treatment assigned to each patient will not be revealed to the Investigator, the patient, or the Sponsor or their designee, until the formal unblinding of 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.

Details of the unblinding process for the interim analysis will be detailed in the SAP and independent DMC Charter documents.

6.8 Replacement of Patients

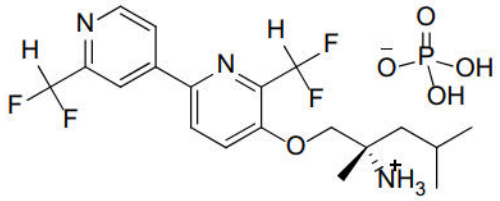
Patients will not be replaced in this study.

7. Treatment

7.1 LX9211 and Matching Placebo

7.1.1 Identity of Active Drug

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 $C_{19}H_{23}F_4N_3O \cdot H_3PO_4$, 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 is being performed in compliance with current Good Manufacturing Practice (GMP) at Wuxi Apptec (Shanghai, China).

The study drug dose form consists of white to off-white round coated tablets containing 10 mg, 20 mg, or 50 mg of LX9211 or a matching placebo. 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.

7.1.2 Packaging, Labeling, and Storage

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

LX9211 20-mg and 10-mg tablets (and matching placebo) are packaged in 30 cc HDPE bottles containing pharma coil and a child resistant polyethylene screw cap with induction seal. Each bottle contains 20 tablets.

LX9211 and matching 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 of all the strength tablets LX9211 (50-mg, 20-mg, and 10-mg) and matching placebo 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 of diabetes, and the patients' DPNP (ie gabapentin, pregabalin, and antidepressant medications).

7.3 Prohibited Medication

- Use of NSAIDS on chronic basis within 2 weeks prior to Screening or at any time for the duration of the study for treatment of DPNP is not permitted.

- Use of opiates in the 2 months prior to Screening or at any time for the duration of the study for treatment of DPNP is not permitted **Note:** Brief use (<1 week) of opioid medication for management of non-DPNP acute pain (eg, tooth extraction/acute injury) at least 1 month prior to the Screening Visit is permitted.

- Cannabidiol, if used for mood or sleep, is acceptable. If used for DPNP it would be allowed if it is the only concomitant medication being taken for DPNP. If it is not the only medication being taken for DPNP, it should be withdrawn at least 1 month prior to Screening.

- Patients may not use additional medications for DPNP other than those medications prescribed for DPNP including pregabalin, gabapentin, and antidepressant medications, which have been taken at stable doses for at least 1 month prior to Screening.

- **Note:** At the Investigator's discretion, patients may take up to 3 grams of acetaminophen per day as rescue medication for DPN pain.

Patients must not have received any investigational agent or study drug within 30 days or 5 half-lives, whichever is longer, prior to Screening or at any time for the duration of the study.

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, 20 mg, and 10 mg) will be supplied in tablet form to be taken orally. A placebo, identical 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 study facility, 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. 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 study facility, 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 study facility on Day 1.

On Day 2 - 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.

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 100 mg/10 mg	2 x 50-mg LX9211 tablets + 2 x Placebo tablets	1 x 10-mg LX9211 tablet, qd
Group 2: 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 3: Placebo	2 x Placebo tablets + 2 x Placebo tablets	1 x Placebo tablet, qd

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 percentage will be calculated as:

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

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 less than 80% or greater than 100%, the Investigator will ask the patient for the reason(s) of non-compliance with the dosing instructions, and clearly record the reason(s) in the source documents and on the eCRF.

If a patient’s compliance is noted to be less than 80% or greater than 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. In the case of tolerability issues, the investigator can consider a temporary dose interruption of no less than 3 days, but no more than 5 days. If adverse event continues once study drug has been reinitiated then patient's continued participation needs to be assessed.

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 Clinical Laboratory Assessment

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.

8.1.2 Pharmacokinetic 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, and 6, just prior to the dosing of study drug on the day of the clinic visit. At the Week 11 visit a final sample will be collected.

The PK substudy will include approximately 30 patients. These patients will be confined to a clinical research unit (CRU) twice during the study for intensive PK evaluation and biomarker evaluation: prior to and following the first dose of study drug and prior to and following their final dose of study drug (planned for Week 6). Pharmacokinetic assessments will be performed at time points indicated in the schedule of events (Appendix B).

Plasma samples will be analyzed by a central bioanalytical laboratory (Covance Laboratories Inc., Madison, WI) under a separate protocol. Detailed procedures for the drawing, preparation, storage, and shipping of samples will be provided to the study site.

8.1.3 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 adverse events 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 with the Medical Monitor.

8.1.3.1 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.

8.1.3.2 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.

8.1.3.3 Electrocardiograms

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

8.1.4 Patient Reported Outcomes

Three patient-reported outcomes (PROs), BPI-DPN, 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 BPI-DPN, is a 9-item questionnaire assesses the severity of pain and its impact on functioning in patients with DPN. The full questionnaire will be completed at Visit 3 (Baseline) and at Visit 4, 5, 6, and 7. Question 5 (average pain of prior 24 hours) and Question 9 F (interference of pain with sleep) will be completed daily from Run-in through the end of the Safety Follow-up Period.

- 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 will be performed at Week 6.

- 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. This will be completed at Visit 3 (Baseline), and at Visits 6 and 7.

8.1.5 Qualitative Patient Interview

A telephone qualitative patient interview substudy will be conducted for approximately 60 patients within 2 weeks following the Week 6 Visit or following premature withdrawal.

The purpose of the phone interview will be to gain insight and understanding of patients' experiences with symptoms of DPNP 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.

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.com

In case of failure of/lack of access to both email and fax, the event should be reported using Physician On-Call 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
Drug Safety Physician
Email: [redacted]
Phone: [redacted]

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

[redacted] MD
[redacted] Clinical Development
Email: [redacted]
Phone: [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 at least 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

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

Sample Size Reestimation

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

To derive the reestimated number of patients at the interim analysis, a simulation will be made that inputs: the observed group mean difference and its common standard deviation, a value for

the maximum total number of patients (E[Max]) equal to 351 patients and, specification that the reestimation rule is the Exact E method. The Exact E method increases the patient number total until the desired conditional power is achieved.

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

10.2 Analysis Populations

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

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 at least 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.

10.2.4 Pharmacokinetics Population (PK)

10.2.4.1 Pharmacokinetics Population (PK) – Substudy

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

10.2.4.2 Pharmacokinetics Population (PK) – C_{trough}

The PK Population for evaluation of C_{trough} will include all patients who received at least 1 dose of study drug and at least 1 C_{trough} 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 Brief Pain Inventory - DPN (BPI-DPN) , the 11-point scale (0 [no pain] to 10 [pain as bad as you can imagine])

10.3.2 Secondary Efficacy Endpoints

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

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

- Change from Baseline to Week 6 in the severity of pain and interference of pain with sleep and other aspects of the patient's life based on the Brief Pain Inventory (BPI) Short Form for diabetic peripheral neuropathy (BPI-DPN) including the following:
    - Pain at its worst
    - Pain at its least
    - Pain right now
    - Total interference score
    - General activity
    - Mood
    - Walking ability
    - Normal work
    - Relations with other people
    - Sleep
    - Enjoyment of life

- Proportion of patients discontinuing treatment due to lack of efficacy defined as increase in ADPS based on Question 5 of the Brief Pain Inventory - DPN (BPI-DPN) from Baseline of 30%

- PGIC at Week 6

- Time to loss of efficacy from Week 6 to Week 11 among patients achieving at least 30% reduction in pain intensity in ADPS based on Question 5 of the Brief Pain Inventory - DPN (BPI-DPN) at Week 6

10.3.3 Other Efficacy Endpoints

Other efficacy endpoints are:

1. Change from Baseline to Week 6 in the Neuropathic Pain Symptom Inventory (NPSI)
2. Change from Baseline to each week in ADPS, based on Question 5 of the BPI-DPN
3. Proportion of patients with ≥30% reduction from Baseline in ADPS, based on Question 5 of the BPI-DPN by week
4. Proportion of patients with ≥50% reduction from Baseline in ADPS, based on Question 5 of the BPI-DPN by week
5. Cumulative distribution function of percent change in ADPS based on Question 5 of the BPI-DPN from Baseline to Week 6 comparing each LX9211 treatment group to placebo
6. Cumulative distribution function of percent change in ADPS based on Question 5 of the BPI-DPN from Week 6 to Week 11 comparing each LX9211 treatment group to placebo

10.3.4 Pharmacokinetic (PK) Endpoints

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

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

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. 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 (%) 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 the rescue medications.

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 BPI-DPN 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: BPI-DPN scores and NPSI, measured at multiple time points, will be analyzed using a similar modeling strategy as used for the primary endpoint.

Categorical secondary endpoints: PGIC, Proportion of responders based on Question 5 of BPI-DPN 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 BPI-DPN 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.

Multiplicity

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

10.4.3 Pharmacokinetic (PK) Analyses

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

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

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

10.4.4 Subgroup Analyses

The primary endpoint will be analyzed by the following patient subgroups:

- 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 22.1.

Treatment emergent adverse events (TEAEs) are defined as events that first occur or worsen 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). 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 into Low, Normal, and 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 laboratory test results will be provided.

10.4.5.4 Vital Signs

Vital signs values, and changes from Baseline to each time point will be summarized using descriptive statistics and presented by treatment group. In addition, vital signs categorized as "Clinically significant" or" Not clinically significant" 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 at least 1 post Baseline 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 50% of the planned information has been accrued. This will occur when the first 141 patients have been accrued and followed to endpoint at Week 6 or dropped out from the trial earlier, whichever event occurs first. Should a patient drop out early in the study, but return for the Week 6 visit, that Week 6 data will be used in the analysis.

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

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	+7
Initiation Activities							
Informed consent	X						
Confirmation of eligibility	X	X	X				
Medical history and demographics	X						
Register patient for Screening in IXRS	X						
Register patient for single-blind Run-in period in IXRS		X					
Register patient for Randomization in IXRS			X				
Procedures/Events							
Complete physical exam **[c]**	X						
Symptom-related brief physical examination **[c]**			X	X	X	X	X
Weight	X	X	X	X	X	X	X
Height	X						
BMI calculation	X						
Patient completes HADS	X						
MNSI (Part B)	X						
Seated vital signs	X		X	X	X	X	X
Orthostatic vitals **[d]**			X				
12-lead ECG **[e]**	X		X			X	X
Assess dose compliance			X	X	X	X	X

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

Exit Interview Substudy Assessments							
Exit interview **[l]**						X	

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

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

14. Appendix B – Substudy of PK on Day 1, Day 2, and Week 6 Visits: Procedure Listing

Week/Visit Window (days)	**Day -1**	**Day 1 (Baseline)**	**Day 2**	**Day prior to Week 6 Or EOT / EW**	**Week 6 Or EOT / EW**	**Week 6 + 1 Day Or EOT / EW**
Check into CRU	X	or predose X		X	or predose X	
Confined to CRU		X			X	
Discharge from CRU			X			X
Abbreviation: CRU = clinical research unit						

PK Sample Collection Times on Day 1, Day 2 (predose), and Week 6 Visits

	Predose	**0.5 hr-**	**1 hr**	**2 hr**	**4 hr**	**6 hr**	**8 hr**	**10 hr**	**12 hr**	**14 hr**	**16 hr**	**Day 2 (predose) and 24 hrs after Week 6 dose**
PK sample collection **[a, b]**	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviation: PK = pharmacokinetics

a. Samples should be collected at the time points ±5 min.

b. PK Substudy samples will be collected at the following time points: Day 1 predose (0 hr), 0.5, 1, 2, 4, 6, 8, 10, 12, 14, and 16 hours postdose; Day 2 predose; Week 6 predose (0 hr), 0.5, 1, 2, 4, 6, 8, 10, 12, 14, 16, and 24 hrs postdose.

15. Appendix C –Biomarker Collections for Patients Participating in Substudy of PK: Procedure Listing

Week/Visit	Day 1 (Baseline)	Day 2	Week 2	Week 4	Day prior to Week 6 Or EOT / EW	Week 6 Or EOT / EW	Week 11 Or 35 Days after EOT / EW
Whole blood for biomarker/target engagement **[a]**	X	X	X	X		X	X
Sample for cytokine/chemokine analysis	X	X	X	X		X	X

Abbreviation: PK = pharmacokinetics

a. Whole blood for biomarker/target engagement and cytokine/chemokine substudy samples will be collected at the following time points: Day 1 predose (0 hr), Day 2 predose (0 hr), Week 2 predose (0 hr), Week 4 predose (0 hr); Week 6 predose (0 hr), and Week 11 predose (0 hr).

16. Appendix D – 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
									TOTAL		**49**

PK and biomarker substudy blood collection	**Week -4**	**Week -2**	**Day 1 (Baseline)**	**Day 2**	**Week 2**	**Week 4**	**Week 6 Or EOT / EW**	**Week 11 Or 35 Days after EOT / EW**	**Total # of Tests**	**Volume /Test (mL)**	**Total Volume (mL)**
PK sample collection			11	1			12		24	4	96
Whole blood for possible biomarker/target engagement			1	1	1	1	1	1	6	3	18
Sample for cytokine/chemokine analysis			1	1	1	1	1	1	6	4	24
									TOTAL		**138**

17. Appendix E – 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;
- 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.

18. Appendix F – 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 subInvestigator 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.

19. Appendix G – Calculations

Cockcroft-Gault equation:

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

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

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.

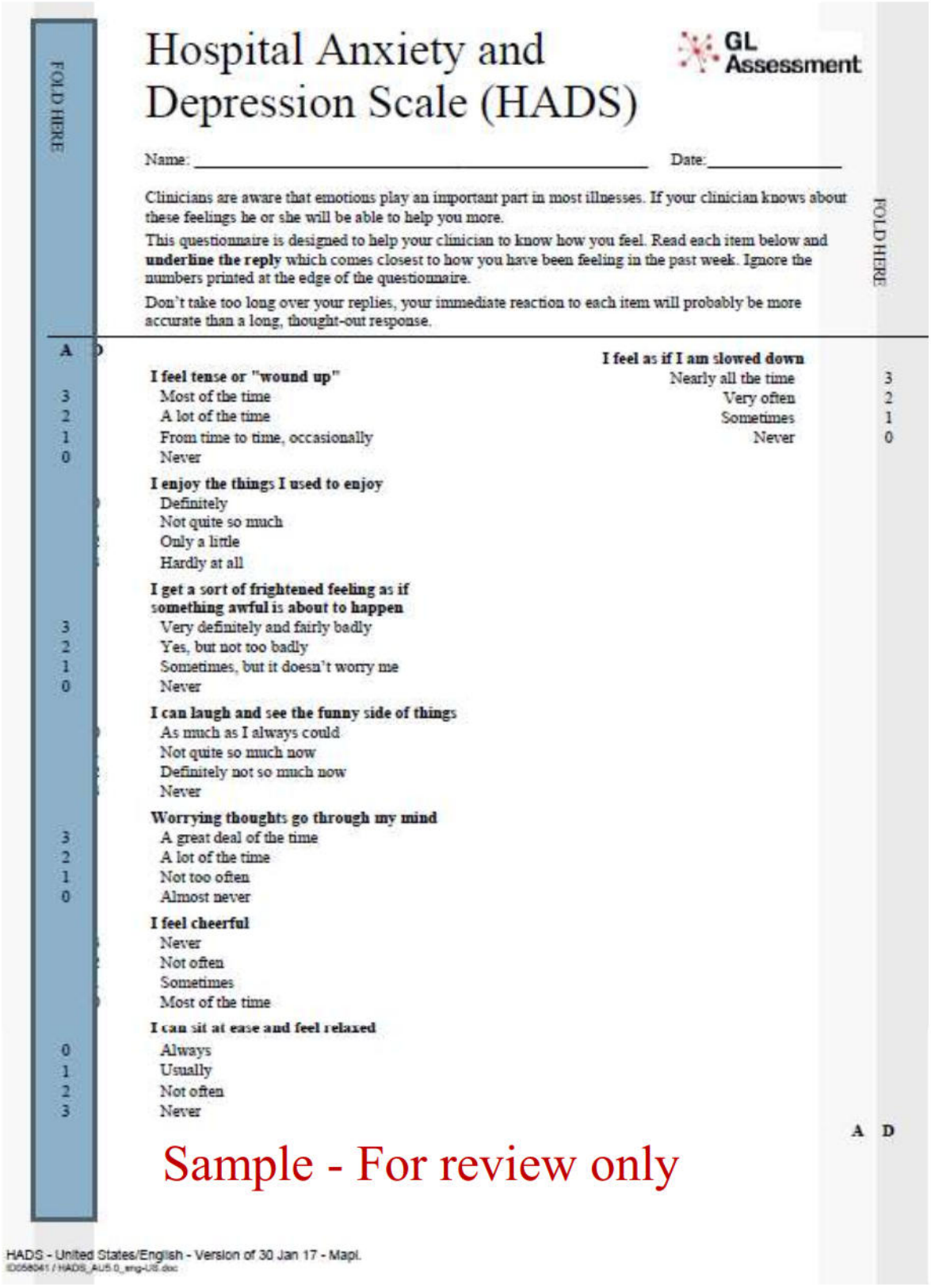
Body Mass Index equation:

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

20. Appendix H – Human 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.

A

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

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

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

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

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

I feel cheerful
Never
Not often
Sometimes
Most of the time

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

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

A D

Sample - For review only

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

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

Please make sure you have answered all the questions.

	A	D
TOTAL		

21. Appendix I – Michigan Neuropathy Screening Instrument (MNSI-Part B)

MICHIGAN NEUROPATHY SCREENING INSTRUMENT

B. Physical Assessment (To be completed by health professional)

1. Appearance of Feet

	Right	Left
a. Normal	☐ 0 Yes ☐ 1 No	Normal ☐ 0 Yes ☐ 1 No
b. If no, check all that apply:		If no, check all that apply:
Deformities	☐	Deformities ☐
Dry skin, callus	☐	Dry skin, callus ☐
Infection	☐	Infection ☐
Fissure	☐	Fissure ☐
Other	☐	Other ☐
specify:	_____	specify: _____

	Right		Left	
2. Ulceration	Absent ☐ 0	Present ☐ 1	Absent ☐ 0	Present ☐ 1

	Right			Left		
3. Ankle Reflexes	Present ☐ 0	Present/ Reinforcement ☐ 0.5	Absent ☐ 1	Present ☐ 0	Present/ Reinforcement ☐ 0.5	Absent ☐ 1
4. Vibration perception at great toe	Present ☐ 0	Decreased ☐ 0.5	Absent ☐ 1	Present ☐ 0	Decreased ☐ 0.5	Absent ☐ 1
5. Monofilament	Normal ☐ 0	Reduced ☐ 0.5	Absent ☐ 1	Normal ☐ 0	Reduced ☐ 0.5	Absent ☐ 1

Signature:_____ Total Score _____ /10 Points

MNSI, © University of Michigan, 2000

22. Appendix J – Brief Pain Inventory Short Form for Diabetic Peripheral Neuropathy (BPI-DPN)

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

Brief Pain Inventory (Short Form) - DPN

Date: ____/____/____ Time: _____

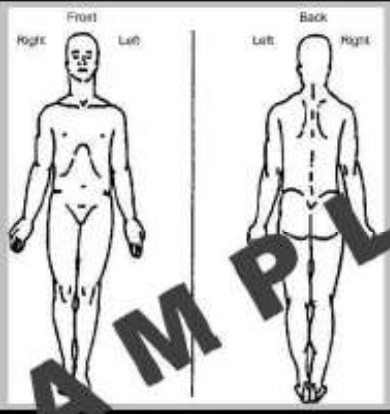
Name: _____ _____ _____

Last First Middle Initial

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

1. Yes 2. No

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



SAMPLE

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

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

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

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

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

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

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

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

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THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

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

Date:___/___/____ Time:_____

Name:_____ _____ _____

Last First Middle Initial

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

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

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

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

A. General Activity

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

B. Mood

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

C. Walking Ability

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

D. Normal Work (includes both work outside the home and housework)

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

E. Relations with other people

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

F. Sleep

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

G. Enjoyment of life

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

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THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

23. Appendix K – Patient Global Impression of Change (PGIC)

PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC)

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

✓ *one box only:*

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

(US/English)

USA/English – Version of 05 April 2005
PGI-C_TG1.0_ID2500-2307_eng-USori.doc

24. Appendix L – Neuropathic Pain Symptom Inventory (NPSI)

NEUROPATHIC PAIN SYMPTOM INVENTORY (NPSI)

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

Date: .....

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

Sex: .....

Age: .....

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

1

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

Q1/. Does your pain feel like burning?

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

Q2/. Does your pain feel like squeezing?

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

Q3/. Does your pain feel like pressure?

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

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

Tick the response that best describes your case.

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

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

Q5/. Does your pain feel like electric shocks?

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

Q6/. Does your pain feel like stabbing?

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

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

Tick the response that best describes your case.

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

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

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

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

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

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

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

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

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

Q11/. Do you feel pins and needles?

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

Q12/. Do you feel tingling?

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

RESULTS

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

25. References

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Lexicon

CLINICAL STUDY PROTOCOL AMENDMENT 3
SUMMARY OF CHANGES

Protocol Number:	LX9211.1-201-DPN LX9211.201 (Abbreviated number)
Investigational Phase:	2
Protocol Title:	A Phase 2, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of LX9211 in the Treatment of Diabetic Peripheral Neuropathic Pain (RELIEF-DPN 1)
Amendment 3 Date:	18 November 2020
Amendment 2.0.1 Date:	09 October 2020
Amendment 2 Date:	28 August 2020
Amendment 1 Date:	17 March 2020
Original Version Date:	05 December 2019
Sponsor:	Lexicon Pharmaceuticals, Inc. 8800 Technology Forest Place The Woodlands, TX 77381-1160 Telephone: (281) 863-3000 Safety Data Facsimile: (832) 442-5462
[redacted]	[redacted] MD Clinical Development Lexicon Pharmaceuticals, Inc. Telephone: [redacted]

Rationale for Amendment

Protocol Amendment 3 includes modifications to inclusion criteria with regards to the study patients' A1C and history of DPN pain. Of note, this protocol amendment provides information about the study's interim analysis and its timing. Additionally, this amendment provides the opportunity to perform administrative changes (typos, etc). The following is a summary of the major changes and the rationale for them.

- Increased allowable A1C value at Screening Visit to 11% to improve patient recruitment
- Broadened the allowable duration of DPN pain to be at least 6 months, with no upper limit of duration to improve recruitment
- Added information with regard to termination of the study based on the interim analysis
- Provided information on when the interim analysis should take place
- Safety Physician contact information has been updated.
- Clarification has been provided regarding when a patient's weight can be taken in relation to their first meal.

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

Page and/or Section	Text in Protocol Amendment 2.0.1	Text in Protocol Amendment 3	Rationale
Footers (Global)			Editorial Change
pg. 1, 2		Amendment 3 date provided	Administrative Change
pg. 4	A1C ≤10.5%	A1C ≤11%	Improve Patient Recruitment
Treatment Schema pg. 7, 34	A1C ≤10.5%	A1C ≤11%	Improve Patient Recruitment
Treatment Schema pg. 7, 34	History of DPNP >6 months to no more than 5 years in duration	History of DPNP ≥6 months	Improve Patient Recruitment
pg. 8		An interim analysis will occur when the first 141 patients have been accrued and followed to endpoint at Week 6. The interim analysis will include formal statistical testing for efficacy, and should the prespecified stopping rule be met, the trial may stop after enrollment of the first 141 patients.	Provide timing information of the interim analysis
pg. 8	Patients will have a diagnosis of T1DM or T2DM with A1C ≤10.5% and a history of >6 months, but not more than 5 years, of chronic DPNP that meets pain criteria at the end of the Run-in Period.	Patients will have a diagnosis of T1DM or T2DM with A1C ≤11% and a history of ≥6 months of chronic DPNP that meet pain criteria at the end of the Run-in Period.	Improve Patient Recruitment
pg. 9, 39	Inclusion # 6: Pain from DPN ranging between at least 6 months to no more than 5 years in duration	Inclusion # 6. Pain from DPN present for at least 6 months	Improve Patient Recruitment
pg. 9, 39	Inclusion #7: At the Screening Visit, A1C must be ≤10.5%.	Inclusion #7: At the Screening Visit, A1C must be ≤11%	Improve Patient Recruitment

Page and/or Section	Text in Protocol Amendment 2.0.1	Text in Protocol Amendment 3	Rationale
Sec 6.4.1		Section Added: Termination of the Study Based on Planned Interim Analysis	Provide information about termination of study based on interim analysis
Sec 6.7		Details of the unblinding process for the interim analysis will be detailed in the SAP and independent DMC Charter documents.	Provide information about unblinding process
Sec 8.1.3.2	Height and weight (without shoes) will be measured as outlined in Appendix A. All weights should be measured prior to the patient's first meal of the day.	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.	Protocol Alignment
Sec 9.4	Safety Physician Contact Information	Updated	Administrative Change
Sec 9.6	An independent Data Safety Monitoring Board (DSMB) will not be utilized for this study, responsibility will remain with the Sponsor.	A DMC will be utilized for this study.	This study will now share a DMC with its companion study in postherpetic neuralgia.
Sec 10.1		nQuery Advisor Advanced Pro software (v8.5.2.0) (Statsols, Rathmaculling West, Cork, Ireland) was used to estimate the sample sizes.	

Page and/or Section	Text in Protocol Amendment 2.0.1	Text in Protocol Amendment 3	Rationale
Sec 10.4.5.7	No formal comparative interim analysis is planned.	An interim analysis of the primary endpoint will be performed to test for efficacy when approximately 50% of the planned information has been achieved. This will occur when the first 141 patients have been accrued and followed to endpoint at Week 6 or dropped out from the trial earlier, whichever event occurs first. Should a patient drop out early in the study, but return for the Week 6 visit, the Week 6 data will be used in the analysis. An O'Brien-Fleming upper boundary will be used to test treatment group differences in the primary endpoint at 50% 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 an overall $\alpha = 0.05$. The sequence of z-scores and respective nominal p-values at the 2 planned information times for each pairwise comparison is 3.281 (p=0.001) and 2.199 (p=0.028). Assessment of other data available at the interim analysis will be used to aid the decision-making process (eg, secondary and other efficacy variables). Details of these analyses will be provided in the SAP and DMC Charter documents.	Provide interim analysis specifications

Rationale for Amendment

Protocol Amendment 2.0.1 includes a number of modifications to properly outline the PK, whole blood for possible biomarker/target engagement, and cytokine/chemokine sample collection. Of note, this protocol amendment reduces the number of total samples and total volume of blood to be collected from a patient during their participation in the PK substudy. Additionally, the patient is given the option to potentially reduce the number of days they are to stay at the site's Clinical Research Unit (CRU). This amendment only applies to sites participating in the PK substudy for LX9211.201. The following is a summary of the major changes and the rationale for them. Attached is a detailed summary of each change included in this Amendment.

- Provided patients participating in PK substudy the opportunity to reduce their duration of stay giving them the option to be admitted to the CRU either the day before the first dose (Day -1) or prior to the first dose of study drug (Day 1). In the same manner, patients can be admitted to the CRU either the day before their Week 6 or EOT/EW visit or prior to administration of study drug (LX9211) dose the day of their Week 6 or EOT/EW visit.
- Modified required PK sample collection time points in the Treatment Schema to align with Appendices A and C
- Removed collection of samples for PK time points: 0.5, 1, 2, 4, 6, 8, 10, 12, 14, 16, 24 hours postdose for Day 2 and Day 3 predose as samples will not provide added scientific benefit to the study
- Appendix B: revised table to included option for predose check-in to CRU on Day 1 (Baseline) Visit and Week 6 or EOT/EW visit.
- Appendix C: Included sample collections for whole blood for biomarker/target engagement and cytokine/chemokine on Day 2, Week 2, Week 4, and Week 11 or 35 Days after EOT/EW visits to align with PK collections time points
- Appendix D: Clarification to the collection of necessary samples on Day 2; updated to reflect reduction in sample collections; and updated volume to reflect reduction in sample collection

Page and/or Section	Text in Protocol Amendment 2	Text in Protocol Amendment 2.0.1 (PK Substudy Sites Only)	Rationale
pg. 7 (Methodology)	The PK substudy, will include approximately 30 patients. These patients will be confined to a clinical research unit (CRU) for Day -1 or Day 1 to Day 2, and Week 6 (2 overnight stays) for intensive blood sampling for LX9211 plasma PK evaluation and possible biomarker analyses.	The PK substudy will include approximately 30 patients. These patients will be confined to a clinical research unit (CRU) twice during the study for intensive PK evaluation and biomarker evaluation: prior to and following the first dose of study drug and prior to and following their final dose of study drug (planned for Week 6).	Clarification in the duration of stay for PK substudy
pg. 7 (Treatment Schema)	**PK Evaluation and possible biomarker analysis (up to 30 patients) –** Day 1 to Day 3 and Week 6 Visit	**PK Evaluation and possible biomarker analysis (up to 30 patients) –** Days 1 and 2, Week 2, Week 4, Week 6 or EOT/EW, Week 11 or 35 Days after EOT/EW	Clarification to necessary PK evaluation and possible biomarker time points
pg. 14 (Pharmacokinetic Substudy Assessments)	For the PK substudy (approximately 30 patients), blood samples will be collected at the following intervals while confined to the CRU:	For the PK substudy (approximately 30 patients), patients will be admitted to the CRU either the day before the first dose (Day -1) or prior to the first dose of study drug (Day 1). Blood samples will be collected at the following time points:	Added clarification in the duration of stay for PK substudy
pg. 14 (Pharmacokinetic Substudy Assessments)	· Day -1: Patients will be admitted to the study facility.	Removed	Editorial Change
pg. 14 (Pharmacokinetic Substudy Assessments)	· Day 2: predose and 0.5, 1, 2, 4, 6, 8, 10, 12, 14, and 16 hours postdose; and 24 hours postdose	· Day 2: predose (24 hrs post Day 1 dose)	Clarification to necessary PK time points for Day 2
pg. 14 (Pharmacokinetic Substudy Assessments)	· Day 3: predose	Removed	Clarification to necessary PK time points for Day 3

Page and/or Section	Text in Protocol Amendment 2	Text in Protocol Amendment 2.0.1 (PK Substudy Sites Only)	Rationale
pg. 14 (Pharmacokinetic Substudy Assessments)	Patients will be discharged following the predose sample collection and administration of the Day 3 dose.	Patients will be discharged following the 24-hour postdose sample collection.	Clarification to day of discharge from study facility (CRU)
pg. 14 (Pharmacokinetic Substudy Assessments)	Patients participating in the PK substudy will also have C_{trough} samples collected at Weeks 2, 4, and 11.	Patients participating in the PK substudy will also have C_{trough} blood samples drawn predose on Day 1 and at Weeks 2, 4, and 6, just prior to the dosing of study drug on the day of the clinic visit. At the Week 11/EOT/EW Safety Follow-up Visit, a final sample will be collected	Added clarification to C_{trough} blood sample collection time points
pg. 37 (Sec 5.1.5)	The PK intensive sampling will occur on Days 1-3 and at the Week 6 clinic visit. Each substudy patient will be confined to the clinical research unit (CRU) from the day prior to dosing (Day -1) through Discharge (Day 3).	These patients will be confined to a clinical research unit (CRU) twice during the study for intensive PK evaluation and biomarker evaluation: prior to and following the first dose of study drug and prior to and following their final dose of study drug (planned for Week 6).	Alignment with Synopsis
pg. 49 (Sec 8.1.2)	These patients will be confined to a clinical research unit (CRU) for Day -1 to Day 3, and Week 6 (3 overnight stays) for intensive blood sampling for LX9211 plasma PK evaluation and possible biomarker analyses.	These patients will be confined to a clinical research unit (CRU) twice during the study for intensive PK evaluation and biomarker evaluation: prior to and following the first dose of study drug and prior to and following their final dose of study drug (planned for Week 6).	Alignment with Synopsis
pg. 74 Appendix B	Day 3 Column	Day 3 Column Removed	Patient to discharge from study facility (CRU) on Day 2

Page and/or Section	Text in Protocol Amendment 2	Text in Protocol Amendment 2.0.1 (PK Substudy Sites Only)	Rationale
pg. 74 Appendix B		or predose Day 1 (Baseline)	Clarification: Patient also has the option to check into study facility (CRU) predose on Day 1
pg. 74 Appendix B		or predose Week 6 or EOT/EW	Clarification: Patient also has the option to check into study facility predose of Week 6 or EOT/EW visit
pg. 74 Appendix B	Day 1: 24 hrs postdose	Removed	Clarification to necessary PK sample collection time points for Day 1
pg. 74 Appendix B	Day 2 predose (0 hr), 0.5, 1, 2, 4, 6, 8, 10, 12, 14, and 16 hrs postdose, and predose (-5 min)	Day 2 (Predose)	Clarification to necessary PK sample collection time points for Day 2
pg. 74 Appendix B	and predose (-5 min) Day 3	Removed	Clarification to necessary PK sample collection time points for Day 3
pg. 74 Appendix C	Day-1 (collection day)	Removal of Day -1 (collection day)	Collection of whole blood for possible biomarker/target engagement and cytokine/chemokine sample to now be performed on Day 1 (Baseline)
pg. 74 Appendix C		Day 3 Column Removed	Removal of Day 3

Page and/or Section	Text in Protocol Amendment 2	Text in Protocol Amendment 2.0.1 (PK Substudy Sites Only)	Rationale
pg. 74 Appendix C		Day 2 collection of samples: Whole blood for possible biomarker/target engagement and cytokine/chemokine analysis	Clarification to the collection of necessary samples on Day 2
pg. 74 Appendix C		Week 2 and Week 4 collection of samples: Whole blood for possible biomarker/target engagement and cytokine/chemokine analysis	Clarification to the collection of necessary samples on Week 2 and Week 4
pg. 74 Appendix C		Week 11 or 35 Days after EOT/EW collection of samples: Whole blood for possible biomarker/target engagement and cytokine/chemokine analysis	Clarification to the collection of necessary samples on Week 11 or 35 Days after EOT/EW
pg. 74 Appendix C pg.75 Appendix D	Whole blood for possible isolation of RBC and/or PBMC	Whole blood for possible biomarker/target engagement	Change in terms
pg. 75 Appendix D		Day 2 Samples included for whole blood for possible biomarker/target engagement and cytokine/chemokine sample	Clarification to the collection of necessary samples on Day 2
pg. 75 Appendix D	Day 2 PK sample collection #: 11	Day 2 PK sample collection #: 1	Updated to reflect reduction in sample collection
pg. 75 Appendix D	PK sample collection Total # of Tests: 35	PK sample collection Total # of Tests: 24	Updated to reflect reduction in sample collection
pg. 75 Appendix D	Whole blood for possible isolation of RBC and/or PBMC and Cytokine / Chemokine Total # of Tests: 5	Whole blood for biomarker/target engagement and cytokine/chemokine Total # of Tests: 6	Updated to reflect change in sample collection

Section and/or Page	Text in Protocol Amendment 2	Text in Protocol Amendment 2.0.1 (PK Substudy Sites Only)	Rationale
pg. 75 Appendix D	Whole blood for possible isolation of RBC and/or PBMC and Cytokine / Chemokine sample Total Volume: 15 mL/ 20 mL	Whole blood for possible biomarker/target engagement and cytokine/chemokine sample Total Volume: 18 mL / 24 mL	Updated volume to reflect for sample collection
pg. 75 Appendix D	Total Overall Volume (All Samples): 175 mL	Total Overall Volume (All Samples): 138 mL	Updated volume to reflect reduction in sample collection

CLINICAL STUDY PROTOCOL AMENDMENT 2
SUMMARY OF CHANGES

Protocol Number:	LX9211.1-201-DPN LX9211.201 (Abbreviated number)
Investigational Phase:	2
Protocol Title:	A Phase 2, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of LX9211 in the Treatment of Diabetic Peripheral Neuropathic Pain (RELIEF-DPN 1)
Original Version Date:	05 December 2019
Amendment 1 Date:	17 March 2020
Amendment 2 Date	28 August 2020
Sponsor:	Lexicon Pharmaceuticals, Inc. 8800 Technology Forest Place The Woodlands, TX 77381-1160 Telephone: (281) 863-3000 Safety Data Facsimile: (832) 442-5917
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Rationale for Amendment

Protocol Amendment 2 includes a number of modifications to inclusion/exclusion criteria, endpoints, prior and concomitant medications, corrects a number of inconsistencies, and includes a number of administrative changes. The following is a summary of the major changes and the rationale for them. Attached is a detailed summary of each change included in this Amendment is attached.

- The name of the Lexicon Medical Director has been changed due to departure of the prior Medical Director from the company.
- The Introduction was updated to include results of Segment 2 reproductive toxicology studies, which support inclusion of women of childbearing potential in the study provided they are using adequate contraception.
- The primary endpoint was modified to be based on the average pain experienced by the patient over the prior 24 hours as measured by the Brief Pain Inventory-Diabetic Peripheral Neuropathy (BPI-DPN) scale, question 5, rather than the Numerical Rating Scale (NRS scale), which was a single item scale that collected the worst pain level over the prior 24 hours. This also changed the basis upon which the Average Daily Pain Score (ADPS) was defined from the NRS to the BPI-DPN. Many other endpoints, which had been based on the worst pain measure in the NRS scale, were also modified to reflect the new measure based on the BPI-DPN. This was done to reduce the amount of variability expected in the scores and provide a better measure of overall potential impact the drug on pain levels.
- Clarified secondary outcome measure to specify that change from Baseline to Week 6 in interference of pain with sleep and other aspects of patients life would be assessed based on the BPI-DPN, rather than stating the analysis would be of "severity and pain interference based on the BPI-DPN". Specified that Question 9F of the BPI-DPN would be administered daily to assess interference of pain with sleep.
- Allowed patients to be removed from Screening and then rescreened in order to begin the Run-in Phase under the revised protocol. This is necessary to ensure that the primary question being asked daily is consistent in the Run-in and randomized treatment period, and that patients are provided the same scales during the Run-in and Randomized treatment periods.
- Clarified that Baseline ADPS would be based on the average scores during the second week of the Run-in Phase (previous protocol version implied that it was a single day score – day before randomization)
- Modified required compliance with diary completion to qualify for randomization during the Run-in Phase from 80% (no more than 1 missed entry per week) to 70% (allowing up to 2 missed entries per week) to facilitate patient enrollment.

- Removed the exclusion criteria for high or low variability in pain scores during the Run-in Phase based on rereview of references and assessment that there are no data to support the benefit of this exclusion in patients with DPNP.
- Allowed inclusion of women of childbearing potential using adequate contraception based on new toxicology data.
- Removed upper age limit for entry to allow elderly patients greater than 75 years to enroll.
- Removed exclusion criterion that prevented enrollment of patients who had greater than 1% change in A1C value over prior 6 months based on lack of evidence that such a change could significantly impact pain and response to study drug.
- Increased allowable A1C value at randomization to 10.5% to improve patient recruitment.
- Revised and clarified allowed medications for DPNP prior to, and during the study (opioids, NSAIDs, over-the-counter medications and herbal supplements, cannabinoids), and vaccinations prior to the study in order to better accommodate patient needs.
- Clarified that biomarker assay was to be performed only in patients participating in intensive PK sampling substudy in order to ensure that samples could be collected, processed, and shipped under required conditions.
- Added to the text that Interview Substudy would be performed in patients who completed the study or who discontinued treatment prematurely. In the prior version, this was only stated in the Schedule of Events in the Appendix.
- Specified that time to loss of efficacy measure was to be analyzed among patients who achieved a 30% reduction in pain from Baseline in order to ensure a meaningful analysis.
- Clarified that no adjustment for pair-wise comparisons would be applied to the secondary outcome measures, and hence these analyses would be considered exploratory.
- Included analysis of percent change in the primary outcome measure from Baseline to Week 6 and from Week 6 to Week 11 using cumulative distribution functions.
- Updated the Treatment Schema in the text and the Schedules of Events in the Appendices to be consistent with the design changes and administrative changes in the protocol.

Section and/or Page	Text in Protocol Amendment 1	Text in Protocol Amendment 2	Rationale
pg. 1, 2	Amendment 2	Section for Amendment 2 added	Administrative Change
pg. 1	Medical Director name change	[redacted] MD	Administrative Change
pg. 1	Medical Director telephone update	[redacted] telephone added	Administrative Change
Global	Footer of document update	28 August 2020	Administrative Change
pg. 2	[redacted] (printed name) update	Updated to [redacted] MD	Administrative Change
pg. 3 (Primary Efficacy Endpoint)	The change from Baseline (Day 1) to Week 6 in Average Daily Pain Score (ADPS), based on the 11-point numerical rating scale (NRS) (0 [no pain] to 10 [worst pain imaginable])	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 Brief Pain Inventory - DPN (BPI-DPN), the 11-point scale (0 [no pain] to 10 [pain as bad as you can imagine])	Clarification to establish Baseline and question associated with Primary Endpoint
pg. 3 (Secondary Efficacy Endpoints)	• Proportion of patients with ≥30% reduction in pain intensity from Baseline to Week 6	• Proportion of patients with ≥30% reduction in pain intensity in ADPS based on Question 5 of the Brief Pain Inventory - DPN (BPI-DPN) from Baseline to Week 6	Clarification that pain would be based on Question 5 of the BPI-DPN
pg. 3 (Secondary Efficacy Endpoints)	• Change from Baseline to Week 6 in the severity and pain interference based on the Brief Pain Inventory (BPI) Short Form for diabetic peripheral neuropathy (BPI-DPN)	• Change from Baseline to Week 6 in the severity of pain and interference of pain with sleep and other aspects of the patient's life based on the Brief Pain Inventory (BPI) Short Form for diabetic peripheral neuropathy (BPI-DPN)	Clarification of what was meant by pain interference in previous version of endpoint
pg. 3 (Secondary Efficacy Endpoints)	• Proportion of patients with ≥50% reduction in pain intensity from Baseline to Week 6	• Proportion of patients with ≥50% reduction in pain intensity in ADPS based on Question 5 of the Brief Pain Inventory - DPN (BPI-DPN) from Baseline to Week 6	Clarification
pg. 3 (Secondary Efficacy Endpoints)	• Proportion of patients discontinuing treatment due to lack of efficacy defined as increase in pain score from Baseline of 30%	• Proportion of patients discontinuing treatment due to lack of efficacy defined as increase in ADPS based on Question 5 of the Brief Pain Inventory - DPN (BPI-DPN) from Baseline of 30%	Clarification that pain would be based on Question 5 of the BPI-DPN

Section and/or Page	Text in Protocol Amendment 1	Text in Protocol Amendment 2	Rationale
pg. 3 (Secondary Efficacy Endpoints)	• Time to loss of efficacy	• Time to loss of efficacy from Week 6 to Week 11 among patients achieving at least 30% reduction in pain intensity in ADPS based on Question 5 of the Brief Pain Inventory - DPN (BPI-DPN) at Week 6	Clarification that pain would be based on Question 5 of the BPI-DPN and that population selected for this analysis would be those with at least 30% reduction in pain from Baseline to Week 6
pg. 3 (Other Efficacy Endpoints)	• Change from Baseline to each week in the ADPS, based on the 11-point NRS	• Change from Baseline to each week in ADPS, based on Question 5 of the BPI-DPN	Clarification that pain would be based on Question 5 of the BPI-DPN
pg. 4 (Other Efficacy Endpoints)	• Proportion of patients with ≥30% reduction in pain intensity from Baseline by week, compared to Baseline	• Proportion of patients with ≥30% reduction from Baseline in ADPS, based on Question 5 of the BPI-DPN from Baseline by week	Clarification that pain would be based on Question 5 of the BPI-DPN
pg. 4 (Other Efficacy Endpoints)	• Proportion of patients with ≥50% reduction in pain intensity from Baseline by week, compared to Baseline	• Proportion of patients with ≥50% reduction from Baseline in ADPS, based on Question 5 of the BPI-DPN by week	Clarification that pain would be based on Question 5 of the BPI-DPN
pg. 4 (Other Efficacy Endpoints)		• Cumulative distribution function of percent change in ADPS based on Question 5 of the BPI-DPN from Baseline to Week 6 comparing each LX9211 treatment group to placebo	New endpoint added
pg. 4 (Other Efficacy Endpoints)		• Cumulative distribution function of percent change in ADPS based on Question 5 of the BPI-DPN from Week 6 to Week 11 comparing each LX9211 treatment group to placebo	New endpoint added
pg. 4 (Methodology)	during Weeks 2, 4, and 6 of the double-blind Treatment period, and Week 11 of the Safety Follow-up Period	during Weeks 2, 4, and 6 of the double-blind Treatment Period, and at Week 11 (ie, at the conclusion of the Safety Follow-up Period).	Clarification

Section and/or Page	Text in Protocol Amendment 1	Text in Protocol Amendment 2	Rationale
pg. 4 (Methodology)	Male and female patients of nonchildbearing potential between 18 and 75 years of age, inclusive, diagnosed with T1DM or T2DM, an A1C ≤10.0%, with chronic DPNP, and who meet all inclusion and no exclusion criteria are eligible for enrollment.	Male and female patients of nonchildbearing potential ages 18 years and older, diagnosed with T1DM or T2DM, an A1C ≤10.5%, with chronic DPNP, and who meet all inclusion and no exclusion criteria are eligible for enrollment.	Eliminated upper age limit and modified upper limit of A1c to be 10.5% to allow greater range of patients enrolled
pg. 4 (Methodology)	Use of any opioid medications for the management of DPNP within the 6 months prior to Screening is not permitted.	Use of any opioid medications for the management of DPNP within the 2 months prior to Screening is not permitted.	Decreased time from last opioid usage based on Investigator feedback.
pg. 5 (Methodology: Run-in Period)	Each evening patients will rate the intensity of their DPNP over the previous 24 hours using the 11-point NRS with 0 representing "no pain at all" and 10 representing "worst pain imaginable" and record it in their daily pain diary.	Each evening patients will rate and record the intensity of their DPNP over the previous 24 hours based on Question 5 of the BPI-DPN by answering the question "Please rate your pain due to your diabetes by indicating the one number that best describes your pain on the average." (0 [no pain] to 10 [pain as bad as you can imagine]) in their daily pain diary and will rate the interference of pain with sleep by answering Question 9F of the BPI-DPN.	Modifies pain assessment to be based on BPI-DPN and specified that sleep will be assessed during the Run-in Period using the DPI-DPN.
pg. 5 (Methodology: Run-in Period)		This derived value of the ADPS over Week 2 will serve as the Baseline measure used for analyses.	Added to define how Baseline value will be established

Section and/or Page	Text in Protocol Amendment 1	Text in Protocol Amendment 2	Rationale
pg. 5 (Methodology: Run-in Period)	In order to qualify for randomization, patients must have completed ≥80% of the daily pain diary entries, meet criteria for moderate to severe pain, meet criteria for acceptable variability in the ADPS, and demonstrate ≥80% compliance with taking the expected amount of placebo tablets during the Run-in Period.	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, meet criteria for acceptable variability in the ADPS, and demonstrate ≥80% compliance with taking the expected amount of placebo tablets during the Run-in Period.	Reducing to 70% requires patients to complete diaries for 5 out of 7 days rather than 6 out of 7 days.
pg. 5 (Methodology: Run-in Period)	**Note:** Patients who fail Screening may be rescreened ONCE after discussion with the Medical Monitor.	**Note:** Patients who fail Screening may be rescreened ONCE after discussion with the Medical Monitor. Patients who begin the Screening period prior to this amendment and who otherwise would qualify for the study may be rescreened again so as to allow them to begin the Run-in Phase following implementation of this amendment.	Allows patients to be rescreened so as to enter the Run-in Period when revised assessment scales have been programmed into the eDiary.
pg. 5 (Methodology: Run-in Period)	Each evening patients will rate and record the intensity of their DPNP over the previous 24 hours based on Question 5 of the BPI-DPN by answering the question "Please rate your pain due to your diabetes by indicating the one number that best describes your pain on the average." (0 [no pain] to 10 [pain as bad as you can imagine]) in their daily pain diary.	Each evening patients will rate and record the intensity of their DPNP over the previous 24 hours based on Question 5 of the BPI-DPN by answering the question "Please rate your pain due to your diabetes by indicating the one number that best describes your pain on the average." (0 [no pain] to 10 [pain as bad as you can imagine]) in their daily pain diary and will rate the interference of pain with sleep by completing Question 9F of the BPI-DPN.	Clarification on how patients should record pain and which "tool" will be used for this assessment and that interference of pain with sleep will be measured during the Run-in Period.

Section and/or Page	Text in Protocol Amendment 1	Text in Protocol Amendment 2	Rationale
pg. 6 (Methodology: Randomization/Double blind Treatment Period)	Each evening during the double-blind Treatment Period, patients will be required to rate and record the severity of their DPNP over the previous 24 hours using an 11-point NRS, record the use of rescue medication (acetaminophen), and rate the interference with sleep.	Each evening patients will rate and record the intensity of their DPNP over the previous 24 hours based on Question 5 of the BPI-DPN by answering the question "Please rate your pain due to your diabetes by indicating the one number that best describes your pain on the average." (0 [no pain] to 10 [pain as bad as you can imagine]), will record the use of rescue medication (acetaminophen), and will rate the interference of pain with sleep using Question 9F of the BPI-DPN.	Clarification on how patients should record pain and which "tool" will be used for this assessment
pg. 6 (Methodology: Randomization/Double blind Treatment Period)	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.	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 of weekly averages.	Clarification
pg. 6 (Methodology: Safety Follow-up Period)	Each evening patients will continue to rate and record the severity of their DPNP over the previous 24 hours using the 11-point NRS, record the use of rescue medication (acetaminophen), and rate the interference with sleep.	Each evening patients will rate and record the intensity of their DPNP over the previous 24 hours based on Question 5 of the BPI-DPN by answering the question "Please rate your pain due to your diabetes by indicating the one number that best describes your pain on the average." (0 [no pain] to 10 [pain as bad as you can imagine]), will record the use of rescue medication (acetaminophen), and will rate the interference of pain with sleep by completing Question 9F of the BPI-DPN.	Modifies pain assessment to be based on BPI-DPN and specified that sleep will be assessed during the Run-in Period using the DPI-DPN.
pg. 6 (Methodology: Safety Follow-up Period)	At the Week 6 visit a final sample will be collected.	At the Week11 EOT/EW Visit a final sample will be collected.	Clarification was listed in Schedule of Events, but not captured in the text

Section and/or Page	Text in Protocol Amendment 1	Text in Protocol Amendment 2	Rationale
pg. 7 (Methodology: Safety Follow-up Period)	The second optional substudy is a qualitative patient interview, which will include approximately 60 patients.	The second optional substudy is a qualitative patient interview following the Week 6 visit (or after early study withdrawal), which will include approximately 60 patients.	Clarification when Patient Interview will occur
pg. 7, 34 (Figure 5.1-1)	18-75 years, inclusive	≥18 years old	Eliminated upper age limit
pg. 7, 34 (Figure 5.1-1)	A1C ≤10.0%	A1C ≤10.5%	Modified to allow greater range of A1C%
pg. 7, 34 (Figure 5.1-1)	3 groups	Convergent line added to demonstrate all groups start Placebo at (Single-blind Safety Follow-up Period)	Clarification
pg. 7, 34 (Figure 5.1-1)	T1DM, T2DM, DPN, NPR	(Acronyms removed)	
pg. 7, 34 (Figure 5.1-1)		@ Day 1 may occur up to 2 weeks plus 3 days after start of the Run-In period	Added
pg. 7, 34 (Figure 5.1-1)	(+/- 7 Day Window)	(+ 7 Day window)	To assure 5 half-lives are met
pg. 7, 34 (Figure 5.1-1)		Windows included at Week 2,4,6,11 time points	Clarification
pg. 8 (Study Population)	Male and female patients of nonchildbearing potential who are ≥18 to ≤75 years of age at the time of Screening will be enrolled. Patients will have a diagnosis of T1DM or T2DM with A1C ≤10.0% and a history of >6 months, but not more than 5 years, of chronic DPNP that meets pain criteria at the end of the Run-in Period.	Male and female patients who are ≥18 years of age at the time of Screening will be enrolled. Patients will have a diagnosis of T1DM or T2DM with A1C ≤10.5% and a history of >6 months, but not more than 5 years, of chronic DPNP that meets pain criteria at the end of the Run-in Period.	Toxicology data now permits women of childbearing potential to join trial with use of appropriate birth control.
pg. 8, 47 Table (treatment group row)		Updated asterisks to be consistent with the footer	Administrative Change

Section and/or Page	Text in Protocol Amendment 1	Text in Protocol Amendment 2	Rationale
pg. 8 (Duration of Treatment)	Patients will be treated 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.	Patients will be treated with placebo or active study drug for 13 weeks (2 weeks of single-blind placebo, 6 weeks of double-blind placebo or LX9211, and 5 weeks of single-blind placebo). Patient participation will be approximately 105 days (assuming no rescreening), 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.	Correction of number of days patients will be treated in the study with either placebo or active drug
pg. 8 (Inclusion #2)	Adult male and female patients ≥18 years of age to < 75 years	Adult male and female patients ≥18 years of age at the Screening Visit	Removed upper age limit to increase enrollment of elderly
pg. 8 (Inclusion #2)	a. Females are to be surgically sterile (documented hysterectomy, tubal ligation, or bilateral salpingo-oophorectomy) or postmenopausal (defined as at least 12 months of spontaneous amenorrhea). If necessary, follicle-stimulating hormone (FSH) results >40 IU/L at Screening are confirmatory in the absence of a clear postmenopausal history.	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®.	Toxicology data now permits women of childbearing potential to join trial with use of appropriate birth control

Section and/or Page	Text in Protocol Amendment 1	Text in Protocol Amendment 2	Rationale
pg. 9 (Inclusion #2) Bolded text has been removed	Nonsterile male patients with sexual partners of childbearing potential must agree to use adequate methods of contraception from Baseline through the Week 11 Visit. **Adequate methods of contraception for the patient or partner 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®; if a patient is not sexually active, but becomes active, he or his partner should use medically accepted forms of contraception.**	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.	Modified to be consistent with wording for women of childbearing potential
Pg. 9 (Inclusion #5)	Michigan Neuropathy Screening Instrument (MNSI) Part B score of ≥2.5 at Screening	Michigan Neuropathy Screening Instrument (MNSI) Part B score of ≥2.5 at Screening based on Items 1-4.	Clarification. Item 5 of MNSI had not been validated.
pg. 9 (Inclusion #7)	At the Screening Visit, A1C must be ≤10.5% with no more than 1% absolute change in A1C (eg, 8% to 9%)in the previous 6 months.	At the Screening Visit, A1C must be ≤10.5%	Removed exclusion of patients who experienced 1% change in past 6 months as being too restrictive

Section and/or Page	Text in Protocol Amendment 1	Text in Protocol Amendment 2	Rationale
pg. 9 (Inclusion #9)	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)	Moderate to severe pain as confirmed by average pain score based on Question 5 of the BPI-DPN recorded in the pain diary in the 14 days prior to randomization (Run-in Period)	Clarification of which question will be used (#5) and what tool will be employed for the assessment
pg. 10 (Exclusion #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	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	Added statement to permit Investigators discretion in excluding patients
pg. 11 (Exclusion #5)	Use of opioid medications for management of DPNP within the 6 months prior to the Screening Visit **Note:** Brief use (< 1 week) of opioid medication for management of non-DPNP acute pain (eg, tooth extraction/ acute injury) at least 1 month prior to screening is permitted.	Use of opioid medications for management of DPNP within the 2 months prior to the Screening Visit. **Note**: Brief use (<1 week) of opioid medication for management of non-DPNP acute pain (eg, tooth extraction/ acute injury) at least 1 month prior to Screening Visit is permitted.	Clarification that brief use of opioids prior to Screening are permitted under defined conditions
pg. 11 (Exclusion #6)	Use of chronic NSAIDs, any investigational oral/topical/injected therapy, or over the counter supplements for management of DPNP within the 3 months prior to the Screening Visit	Use of NSAIDs less than 2 weeks prior to the Screening Visit	Reduce time for NSAID exposure prior to Screening

Section and/or Page	Text in Protocol Amendment 1	Text in Protocol Amendment 2	Rationale
pg. 11 (Exclusion #7)	A positive urine drug test for drugs of abuse and cannabinoids.	A positive urine drug test for drugs of abuse and cannabinoids. **Note:** Cannabidiol if used for mood or sleep is acceptable. If used for DPNP it would be allowed if it is the only concomitant medication being taken for DPNP. If not the only medication being taken for DPNP, it should be withdrawn at least 1 month prior to Screening.	Clarification of cannabinoid use
pg. 11 (Exclusion #12)	Receipt of any investigational agent or study drug within 30 days or 5 half-lives, whichever is longer, prior to Baseline	Receipt of any investigational agent or study drug within 30 days or 5 half-lives, whichever is longer, prior to Screening	Clarification
pg. 12 (Exclusion #13)	Receipt of any protein, antibody/biologic- or antibody-based agents (eg, growth hormones or monoclonal antibodies) within 3 months prior to dosing on planned Day 1. **Note:** Influenza vaccine will be allowed if administered >21 days prior to dosing.	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:** Prophylactic vaccines, such as influenza, pneumococcal, or TDAP vaccine will be allowed if administered >7 days prior to randomization.	Permits greater use of prophylactic vaccines
pg. 12 (Exclusion #18)	History of any major surgery within 6 months prior to Baseline or surgery that is anticipated to be performed during the study period	History of any major surgery within 3 months prior to Baseline or surgery that is anticipated to be performed during the study period	Reduced duration for postoperative recovery prior to Baseline
pg. 13 (Exclusion #27)	Unacceptable variability in the ADPS at the end of the 2 week Run-in Period (as assessed by the standard deviation)	Removed for Amendment 2	Removed for Amendment 2 (see text of SOC for explanation)

Section and/or Page	Text in Protocol Amendment 1	Text in Protocol Amendment 2	Rationale
pg. 13 (Statistical Methods)	A sample size of 75 patients per treatment group who complete the 6-week Double-blind Treatment Period will yield 80% power to detect a true mean difference of 1 unit between at least 1 of LX9211 treatment groups and placebo in ADPS change from Baseline, assuming a common standard deviation of 2 and an overall significance level of α=0.05 (2-sided Dunnett's test). Accounting for a dropout rate of 20%, a total of 282 patients (94 patients per treatment group) will be enrolled and randomly assigned to treatment in a 1:1:1 ratio.	A sample size of 75 patients per treatment group who complete the 6-week Double-blind Treatment Period will yield 80% power to detect a true mean difference of 1 unit between at least 1 LX9211 treatment group and placebo in ADPS change from Baseline to Week 6, assuming a common standard deviation of 2 and an overall significance level of α=0.05 (2-sided Dunnett's test). Accounting for a uniform dropout rate of 20%, a total of 282 patients (94 patients per treatment group) will be enrolled and randomly assigned to treatment in a 1:1:1 ratio.	Clarification
pg. 13 (Statistical Methods)	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 in mean ADPS).	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.	Clarification
pg. 14 (Statistical Methods)	PGIC and the proportion of responders based on the 11-point NRS will be compared between treatments using a Cochran-Mantel-Haenszel test stratified by the randomization factor of Baseline pain severity.	PGIC and the proportion of responders based on Question 5 of the BPI-DPN, 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.	Clarification
pg. 14 (Pharmacokinetic Substudy Assessments)	• Day -1: Patients will be admitted to the CRU	• Day -1: Patients will be admitted to the study facility.	Clarification

Section and/or Page	Text in Protocol Amendment 1	Text in Protocol Amendment 2	Rationale
pg. 20	25. Appendix M	25. Appendix M (Removed)	NRS no longer used in study
pg. 20	26. References	25. References (Updated #)	Administrative Change
pg. 21 (List of Abbreviations and Definitions of Terms)		BPI - Brief Pain Inventory	Abbreviation and Definition added
pg. 22 (List of Abbreviations and Definitions of Terms)	NRS numerical rating score		Abbreviation and Definition removed
pg. 27 (Sec 3.2.5)		In embryo-fetal development studies, the NOAEL for LX9211 phosphate was determined to be 10 mg/kg/day in the rat and 4 mg/kg/day in the rabbit.	Toxicology Information Added
pg. 29 (Sec 3.2.8)		Embryo-Fetal Development Study in Rats: In the rat embryo-fetal development study, doses of LC9211 phosphate evaluated were 0, 1, 3, and 10 mg/kg/day. Test article-related non-adverse effects included decreased mean body weight, body weight, decreased food consumption, reduced adjusted fetal weight and unossified phalanx hindlimb skeletal variations. No test article-related effects on maternal clinical or macroscopic observations, reproductive performance, or fetal external, visceral or skeletal malformations were noted.	Toxicology: Embryo-Fetal Development Study in Rats Section Added
pg. 29 (Sec 3.2.9)		Embryo-Fetal Development Study in Rabbits: In the rabbit embryo-fetal development study, 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.	Toxicology: Embryo-Fetal Development Study in Rabbits Section Added

Section and/or Page	Text in Protocol Amendment 1	Text in Protocol Amendment 2	Rationale
pg. 32 (Sec 4.3)	• Change from Baseline in the Neuropathic Pain Symptom Inventory (NPSI) and to each week in the average daily pain score (ADPS), based on the 11-point NRS	• Change from Baseline in the Neuropathic Pain Symptom Inventory (NPSI) and to each week in the average daily pain score (ADPS), based on Question 5 of the Brief Pain Inventory - DPN (BPI-DPN)	Clarification on tool and question
pg. 33 (Sec 5.1)	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.	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 at Week 11 (Week 5 of the single-blind Safety Follow-up Period).	Clarification
pg. 33 (Sec 5.1)	Male and female patients of nonchildbearing potential, between 18 and 75 years of age, inclusive, diagnosed with T1DM or T2DM and with chronic DPNP, and who meet all inclusion and no exclusion criteria are eligible for enrollment.	Male and female patients of nonchildbearing potential, age 18 years and above, diagnosed with T1DM or T2DM and with chronic DPNP, and who meet all inclusion and no exclusion criteria are eligible for enrollment.	Removal of upper age limit to allow wider age range of patients enrolled
pg. 33 (Sec 5.1)	Use of any opioid medications for the management of DPNP within the 6 months prior to Screening is not permitted.	Use of any opioid medications for the management of DPNP within the 2 months prior to Screening is not permitted.	Reduced exclusion based on prior use of opioids to 2 months from 6 months to address Investigator's observations that 6 months was overly conservative

Section and/or Page	Text in Protocol Amendment 1	Text in Protocol Amendment 2	Rationale
pg. 35 (Sec 5.1.1)	Following confirmation of eligibility criteria, patients will enter the following study periods.	Following confirmation of eligibility criteria, patients will enter the Run-in Period. **Note:** Patients who fail Screening may be rescreened ONCE after discussion with the Medical Monitor. Patients who begin the Screening Period prior to this amendment and who otherwise would qualify for the study may be rescreened again so as to allow them to begin the Run-in Phase following implementation of this amendment.	Added benefit for patients who may have screen failed under Amendment 1 for one of the reasons that are now being modified.
pg. 35 (Sec 5.1.2)	Each evening, patients will rate the intensity of their DPNP over the previous 24 hours using the 11-point NRS where 0 represents "no pain at all" and 10 represents "worst pain imaginable" and record it in their daily pain diary.	Each evening patients will rate and record the intensity of their DPNP over the previous 24 hours based on Question 5 of the BPI-DPN by answering the question "Please rate your pain due to your diabetes by indicating the one number that best describes your pain on the average." (0 [no pain] to 10 [pain as bad as you can imagine]) in their daily pain diary and will rate the interference of pain with sleep by completing Question 9F of the BPI-DPN.	Modifies pain assessment to be based on BPI-DPN and specified that sleep will be assessed during the Run-in Period using the DPI-DPN.
pg. 35 (Sec 5.1.2)	The ADPS will be calculated using all available daily pain diary data. In order to qualify for randomization, patients must have completed ≥80% of the daily pain diary entries, meet criteria for moderate to severe pain, meet criteria for acceptable variability in the ADPS, and demonstrate ≥80% compliance with taking the expected amount of placebo tablets during the Run-in Period.	The ADPS will be calculated using all available daily pain diary data. In order to qualify for randomization, patients must have completed ≥70% of the daily pain diary entries during the week prior to randomization, meet criteria for moderate to severe pain, meet criteria for acceptable variability in the ADPS, and demonstrate ≥80% compliance with taking the expected amount of placebo tablets during the Run-in Period.	Allows patients to be randomized if the miss 2 daily assessments in the week prior to the end of the Run-in Period, rather than only 1 assessment. This is intended to be less restrictive but will still ensure adequate compliance.

Section and/or Page	Text in Protocol Amendment 1	Text in Protocol Amendment 2	Rationale
pg. 36 (Sec 5.1.3)	Each evening during the double-blind Treatment Period, patients will be required to rate and record the severity of their DPNP over the previous 24 hours using an 11-point NRS, record the use of rescue medication (acetaminophen), and rate the interference with sleep.	Each evening patients will rate and record the intensity of their DPNP over the previous 24 hours based on Question 5 of the BPI-DPN by answering the question "Please rate your pain due to your diabetes by indicating the one number that best describes your pain on the average." (0 [no pain] to 10 [pain as bad as you can imagine]), record the use of rescue medication (acetaminophen), and rate the interference of the patient's pain with sleep based on Question 9F of the DPI-PHN.	Modifies pain assessment to be based on BPI-DPN and specified that sleep will be assessed during the Run-in Period using the DPI-DPN.
pg. 36 (Sec 5.1.3)	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.	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 of weekly averages.	Clarification: Added "of weekly averages".
pg. 38 (Sec 6.1- Inclusion #2)	2.Adult male and female patients ≥18 years of age to < 75 years	2. Adult male and female patients ≥18 years of age at the Screening Visit	Removed upper age limit to increase enrollment of elderly.
pg. 38 (Sec 6.1- Inclusion #2)	a. Females are to be surgically sterile (documented hysterectomy, tubal ligation, or bilateral salpingo-oophorectomy) or postmenopausal (defined as at least 12 months of spontaneous amenorrhea). If necessary, follicle-stimulating hormone (FSH) results >40 IU/L at Screening are confirmatory in the absence of a clear postmenopausal history.	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®.	Toxicology data now permits women of childbearing potential to join trial with use of appropriate birth control.

Section and/or Page	Text in Protocol Amendment 1	Text in Protocol Amendment 2	Rationale
pg. 38 (Sec 6.1- Inclusion #2) Bolded text has been removed	Nonsterile male patients with sexual partners of childbearing potential must agree to use adequate methods of contraception from Baseline through the Week 11 Visit. **Adequate methods of contraception for the patient or partner 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®; if a patient is not sexually active, but becomes active, he or his partner should use medically accepted forms of contraception.**	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.	Modified to be consistent with wording for women of childbearing potential
pg. 38 (Sec 6.1 - Inclusion #5)	Michigan Neuropathy Screening Instrument (MNSI) Part B score of ≥2.5 at Screening	Michigan Neuropathy Screening Instrument (MNSI) Part B score of ≥2.5 at Screening based on Items 1-4	Clarification. Item 5 of MNSI had not been validated.
pg. 39 (Sec 6.1 - Inclusion #7)	At the Screening Visit, A1C must be ≤10.5% with no more than 1% absolute change in A1C (eg, 8% to 9%)in the previous 6 months.	At the Screening Visit, A1C must be ≤10.5%.	Removed exclusion of patients who experienced 1% change in past 6 months as being too restrictive

Section and/or Page	Text in Protocol Amendment 1	Text in Protocol Amendment 2	Rationale
pg. 39 (Sec 6.1 - Inclusion #9)	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)	Moderate to severe pain as confirmed by average pain score based on Question 5 of the BPI-DPN recorded in the pain diary in the 14 days prior to randomization (Run-in Period)	Clarification of which question will be used (#5) and what tool will be employed for the assessment
pg. 39 (Sec 6.2 - Exclusion #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	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	Added statement to permit Investigators discretion in excluding patients
pg. 40 (Sec 6.2 - Exclusion #5)	Use of opioid medications for management of DPNP within the 6 months prior to the Screening Visit **Note:** Brief use (< 1 week) of opioid medication for management of non-DPNP acute pain (eg, tooth extraction/ acute injury) at least 1 month prior to screening is permitted.	Use of opioid medications for management of DPNP within the 2 months prior to the Screening Visit. **Note:** Brief use (<1 week) of opioid medication for management of non-DPNP acute pain (eg, tooth extraction/ acute injury) at least 1 month prior to screening is permitted.	Clarification that brief use of opioids prior to screening are permitted under defined conditions
pg. 40 (Sec 6.2 - Exclusion #6)	Use of chronic NSAIDs, any investigational oral/topical/injected therapy, or over the counter supplements for management of DPNP within the 3 months prior to the Screening Visit	Use of NSAIDs less than 2 weeks prior to the Screening Visit	Reduce time for NSAID exposure prior to screening

Section and/or Page	Text in Protocol Amendment 1	Text in Protocol Amendment 2	Rationale
pg. 40 (Sec 6.2 - Exclusion #7)	A positive urine drug test for drugs of abuse and cannabinoids.	A positive urine drug test for drugs of abuse and cannabinoids. **Note:** Cannabidiol, if used for mood or sleep, is acceptable. If used for DPNP it would be allowed if it is the only concomitant medication being taken for DPNP. If not the only medication being taken for DPNP, it should be withdrawn at least 1 month prior to Screening,	Clarification of cannabinoid use
pg. 40 (Sec 6.2 - Exclusion #12)	Receipt of any investigational agent or study drug within 30 days or 5 half-lives, whichever is longer, prior to Baseline	Receipt of any investigational agent or study drug within 30 days or 5 half-lives, whichever is longer, prior to Screening	Clarification
pg. 40 (Sec 6.2 - Exclusion #13)	Receipt of any protein, antibody/biologic- or antibody-based agents (eg, growth hormones or monoclonal antibodies) within 3 months prior to dosing on planned Day 1. **Note:** Influenza vaccine will be allowed if administered >21 days prior to dosing.	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:** Prophylactic vaccines, such as influenza, pneumococcal, or TDAP vaccine will be allowed if administered >7 days prior to randomization.	Permits greater use of prophylactic vaccines
pg. 41 (Sec 6.2 - Exclusion #18)	History of any major surgery within 6 months prior to Baseline or surgery that is anticipated to be performed during the study period	History of any major surgery within 3 months prior to Baseline or surgery that is anticipated to be performed during the study period	Reduced duration for postoperative recovery prior to baseline
pg. 41 (Sec 6.2 - Exclusion #27)	Unacceptable variability in the ADPS at the end of the 2 week Run-in Period (as assessed by the standard deviation)	Removed for Amendment 2	Removed for Amendment 2 (see text for explanation)

Section and/or Page	Text in Protocol Amendment 1	Text in Protocol Amendment 2	Rationale
pg. 43 (Sec 6.7)	In this double-blinded 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.	In this double-blinded study, the designated treatment assigned to each patient will not be revealed to the Investigator, the patient, or the Sponsor or their designee, until the formal unblinding of the study.	Clarification around when unblinding can occur
pg. 44 (Sec 7.1)	LX9211	LX9211 and Matching Placebo	Section headers fixed for consistency
pg. 44 (Sec 7.1)	Identity	Identity of Active Drug	Section headers fixed for consistency
pg. 45 (Sec 7.3)	Use of NSAIDS on chronic basis from 3 months prior to screening or at any time for the duration of the study for treatment of DPNP is not permitted.	• Use of NSAIDS on chronic basis within 2 weeks prior to Screening or at any time for the duration of the study for treatment of DPNP is not permitted.	Reduced duration of prior exposure to NSAID exposure prior to Screening
pg. 45 (Sec 7.3)	Use of opiates in the 6 months prior to screening or at any time for the duration of the study for treatment of DPNP is not permitted.	• Use of opiates in the 2 months prior to Screening or at any time for the duration of the study for treatment of DPNP is not permitted **Note:** Brief use (<1 week) of opioid medication for management of non-DPNP acute pain (eg, tooth extraction/acute injury) at least 1 month prior to the Screening Visit is permitted.	Reduced duration of prior exposure to opioid to 2 months
pg. 46 (Sec 7.3)		• Cannabidiol, if used for mood or sleep, is acceptable. If used for DPNP it would be allowed if it is the only concomitant medication being taken for DPNP. If it is not the only medication being taken for DPNP, it should be withdrawn at least 1 month prior to Screening.	Clarified use of cannabidiols use

Section and/or Page	Text in Protocol Amendment 1	Text in Protocol Amendment 2	Rationale
pg. 46 (Sec 7.3)		• Patients may not use additional medications for DPNP other than those medications prescribed for DPNP including pregabalin, gabapentin, and antidepressant medications, which have been taken at stable doses for at least 1 month prior to Screening.	Added
pg. 46 (Sec 7.3)		• **Note:** At the Investigator's discretion, patients may take up to 3 grams of acetaminophen per day as rescue medication for DPN pain.	Clarification in Prohibited Meds Section
pg. 46 (Sec 7.3)		Patients must not have received any investigational agent or study drug within 30 days or 5 half-lives, whichever is longer, prior to Screening or at any time for the duration of the study.	Clarification statement in prohibited meds section
pg. 49 (Sec 8.1.2)	Plasma samples from all patients will be analyzed for LX9211 C_{trough}.	Blood samples for the determination of plasma LX9211 trough levels (C_{trough}) will be drawn predose on Day 1 and at Weeks 2, 4, and 6, just prior to the dosing of study drug on the day of the clinic visit. At the Week 11 visit a final sample will be collected.	Describes more fully when samples will be collected
pg. 49 (Sec 8.1.2)	Patients enrolled in the optional PK and biomarkers substudy will undergo a more intensive sampling to evaluate the full PK profile of LX9211	Approximately 30 patients enrolled in the optional PK and biomarkers substudy will undergo a more intensive sampling to evaluate the full PK profile of LX9211.	Describes number of patients participating in substudy
pg. 49 (Sec 8.1.2)		These patients will be confined to a clinical research unit (CRU) for Day -1 to Day 3, and Week 6 (3 overnight stays) for intensive blood sampling for LX9211 plasma PK evaluation and possible biomarker analyses.	Clarification on duration of stays for PK substudy

Section and/or Page	Text in Protocol Amendment 1	Text in Protocol Amendment 2	Rationale
pg. 50 (Sec 8.1.4)	The BPI-DPN, a 9-item questionnaire assesses the severity of pain and its impact on functioning in patients with DPN.	• The BPI-DPN, is a 9-item questionnaire assesses the severity of pain and its impact on functioning in patients with DPN. The full questionnaire will be completed at Visit 3 (Baseline) and at Visit 4, 5, 6, and 7. Question 5 (average pain of prior 24 hours) and Question 9F (interference of pain with sleep) will be completed daily from Run-in through the end of the Safety Follow-up Period.	Added specificity when assessments would occur
pg. 50 (Sec 8.1.4)	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 PGIC, a 7-point rating scale will assess patient's belief about the overall improvement experienced by the patient at the end of treatment will be performed at Week 6.	Added specificity when this would occur
pg. 51 (Sec 8.1.4)	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.	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. This will be completed at Visit 3 (Baseline), and at Visits 6 and 7.	Added specificity when this would occur
pg. 51 (Sec 8.1.5)	A telephone qualitative patient interview substudy will be conducted for approximately 60 patients within 2 weeks following the Week 6 Visit.	A telephone qualitative patient interview substudy will be conducted for approximately 60 patients within 2 weeks following the Week 6 Visit or following premature withdrawal.	Clarification on when Patient Interview will occur
pg. 59 (Sec 10.3.1)	• The change from Baseline (Day 1) to Week 6 in Average Daily Pain Score (ADPS), based on the 11-point numerical rating scale (NRS) (0 [no pain] to 10 [worst pain imaginable])	• 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 Brief Pain Inventory - DPN (BPI-DPN), the 11-point scale (0 [no pain] to 10 [pain as bad as you can imagine])	Modifies scale to be used for ADPS

Section and/or Page	Text in Protocol Amendment 1	Text in Protocol Amendment 2	Rationale
pg. 59 (Sec 10.3.2)	• Proportion of patients with ≥30% reduction in pain intensity from Baseline to Week 6	• Proportion of patients with ≥30% reduction in pain intensity in ADPS based on Question 5 of the Brief Pain Inventory - DPN (BPI-DPN) from Baseline to Week 6	Modifies scale to be used for ADPS
pg. 59 (Sec 10.3.2)	• Proportion of patients with ≥50% reduction in pain intensity from Baseline to Week 6	• Proportion of patients with ≥50% reduction in pain intensity in ADPS based on Question 5 of the Brief Pain Inventory - DPN (BPI-DPN) from Baseline to Week 6	Modifies scale to be used for ADPS
pg. 59 (Sec 10.3.2)	• Change from Baseline to Week 6 in the severity and pain interference based on the Brief Pain Inventory (BPI) Short Form for diabetic peripheral neuropathy (BPI-DPN)	• Change from Baseline to Week 6 in the severity of pain and interference of pain with sleep and other aspects of the patient's life based on the Brief Pain Inventory (BPI) Short Form for diabetic peripheral neuropathy (BPI-DPN) including the following:	Clarification on how patients should record pain and which "tool" will be used for this assessment
pg. 59 (Sec 10.3.2)	• Proportion of patients discontinuing treatment due to lack of efficacy defined as increase in pain score from Baseline of 30%	• Proportion of patients discontinuing treatment due to lack of efficacy defined as increase in ADPS based on Question 5 of the Brief Pain Inventory - DPN (BPI-DPN) from Baseline of 30%	Modifies scale to be used for pain assessment
pg. 60 (Sec 10.3.2)	• Time to loss of efficacy	• Time to loss of efficacy from Week 6 to Week 11 among patients achieving at least 30% reduction in pain intensity in ADPS based on Question 5 of the Brief Pain Inventory - DPN (BPI-DPN) at Week 6	Clarification that pain would be based on Question 5 of the BPI-DPN and that population selected for this analysis would be those with at least 30% reduction in pain from Baseline to Week 6.
pg. 60 (Sec 10.3.3)	Change from Baseline to each week in ADPS, based on the 11-point NRS	Change from Baseline to each week in ADPS, based on Question 5 of the BPI-DPN	Modifies scale to be used for ADPS
pg. 60 (Sec 10.3.3)	Proportion of patients with ≥30% reduction in pain intensity by week, compared to Baseline	Proportion of patients with ≥30% reduction from Baseline in ADPS, based on Question 5 of the BPI-DPN by week	Modifies scale to be used for ADPS

Section and/or Page	Text in Protocol Amendment 1	Text in Protocol Amendment 2	Rationale
pg. 60 (Sec 10.3.3)	Proportion of patients with ≥50% reduction in pain intensity by week, compared to Baseline	Proportion of patients with ≥50% reduction from Baseline in ADPS, based on Question 5 of the BPI-DPN by week	Clarification
pg. 60 (Sec 10.3.3)		Cumulative distribution function of percent change in ADPS based on Question 5 of the BPI-DPN from Baseline to Week 6 comparing each LX9211 treatment group to placebo	Added
pg. 60 (Sec 10.3.3)		Cumulative distribution function of percent change in ADPS based on Question 5 of the BPI-DPN from Week 6 to Week 11 comparing each LX9211 treatment group to placebo	Added
pg. 62 (Sec 10.4.2.1)	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 in mean ADPS)	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 BPI-DPN instrument).	Clarifies what scale is to be used for ADPS
pg. 63 (Sec. 10.4.2.2)	Categorical secondary endpoints: PGIC, Proportion of responders based on the 11-point NRS will be compared between treatments using a Cochran-Mantel-Haenszel test stratified by the randomization factor of Baseline pain severity.	Categorical secondary endpoints: PGIC, Proportion of responders based on Question 5 of BPI-DPN will be compared between treatment groups using a Cochran-Mantel-Haenszel test stratified by the randomization factor of Baseline pain severity.	Corrects scale to be used for primary endpoint
pg. 63 (Sec. 10.4.2.2)	The Kaplan-Meier methods will be used to generate statistical summaries of the time to loss of efficacy defined as reduction in pain intensity less than 30%.	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 BPI-DPN from Week 6 to Week 11.	Identifies the population of patients in whom the analysis would be most meaningful

Section and/or Page	Text in Protocol Amendment 1	Text in Protocol Amendment 2	Rationale
pg. 63 (Sec. 10.4.2.2)		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.	Added as this is a Proof of Concept Study.
pg. 65 (Sec. 10.4.5.4)	Vital signs values, and changes from Baseline will be summarized using descriptive statistics and presented by treatment group.	Vital signs values, and changes from Baseline to each time point will be summarized using descriptive statistics and presented by treatment group.	Clarification
pg. 65 (Sec. 10.4.6.1)	Protocol deviation wording	Updated protocol language to be consistent with protocol shell	Added
pg. 65 (Sec. 11.2)	Protocol deviation wording	Updated protocol language to be consistent with protocol shell	Added
pg. 72 (SoE table)	Patient completes NRS on e-Diary	Patient completes Questions 5 and 9F of BPI-DPN on e-diary each day and records rescue medication	Modified based on changes to primary endpoint and specifies scale to be used for sleep assessment
pg. 72 (SoE table)	Patient completes the BPI-DPN	Patient completes the full BPI-DPN	Clarification
pg. 74 Appendix C		Appendix C- Title changed to Biomarker Collections for Patients Participating in Substudy of PK: Procedure Listing	Clarifies that only patients participating in intensive PK sampling will be providing samples for biomarker study
pg. 74 Appendix C		Appendix C - Table has been simplified (edited headers and removed footers)	Clarification
pg. 93 Appendix	Appendix M - NRS Scale	Appendix M - NRS Scale (Removed)	Removed due to change in scale used for ADPS

Lexicon

CLINICAL STUDY PROTOCOL AMENDMENT 1
SUMMARY OF CHANGES

Protocol Number:	LX9211.1-201-DPN LX9211.201 (Abbreviated number)
Investigational Phase:	2
Protocol Title:	A Phase 2, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of LX9211 in the Treatment of Diabetic Peripheral Neuropathic Pain (RELIEF-DPN 1)
Original Version Date:	05 December 2019
Amendment 1 Date:	17 March 2020
Sponsor:	Lexicon Pharmaceuticals, Inc. 8800 Technology Forest Place The Woodlands, TX 77381-1160 Telephone: (281) 863-3000 Safety Data Facsimile: (832) 442-5917
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Rationale for Amendment

Protocol Amendment 1 addresses the following:

a) Added RELIEF-DPN 1 study name reference
b) Synopsis – remove restriction of no rescreening of patients who fail the Run-in Period; Section 5.1 added missing statement from synopsis indicating patients who fail Screening may be rescreened ONCE after discussion with the Medical Monitor
c) Pharmacokinetic Substudy - change from enroll "up to" 30 patients to enroll "approximately" 30 patients
d) Inclusion criterion #7 – change upper limit of A1C to 10.5%; clarify no more than a 1% absolute change in A1C (eg, from 8% to 9%) in the previous 6 months
e) Exclusion criterion #5 - clarify brief use of opioids to be allowed at least 1 month prior to Screening
f) Exclusion criterion #6 – modify to align with Section 7.3 Prohibited Medications
g) Add Exclusion Criterion #27 for unacceptable high or low variability in subject reported pain scores during the Run-in period
h) Section 3.2.6 preclinical GLP-Compliant Toxicology Studies in Rats - Per FDA nonclinical review request, provide additional information from 13-week rat toxicology study
i) Section 3.2.7 Preclinical GLP-Compliant Toxicology Study in Dogs – update section describing 13-week study to include information regarding findings of muscle degeneration in the urinary bladder per FDA request.
j) Section 3.3 Clinical Trials of LX9211 in Humans – add statement of no clinically significant comprehensive metabolic panel (CMP) or urinalysis findings, or bladder dysfunction-related AEs were reported in any subject treated with LX9211 in the SAD or MAD studies.
k) Figure 5.1-1 Treatment Schema moved from Section 5.1.5 Optional Substudies to Section 5.1 Study Design
l) Section 5.1.4 Safety Follow-up Period – Clarify rescue medication to be acetaminophen
m) Section 7.1.2 Packaging, Labeling, and Storage – Remove statement "Study drug supply for the Run-in, Treatment and Safety Follow-up Periods will be labeled accordingly." as labels do not include study periods
n) Section 7.3 Prohibited Medication – added "**Note:** Brief use (<1 week) of opioid medication for management of non-DPNP acute pain (eg, tooth extraction/acute injury) at least 1 month prior to Screening Visit is permitted." to align with Exclusion criteria #5
o) Section 8.1.3.1 Vital Sign Measurements – clarify vital signs should be collected with the patient in a seated position; also added to Schedule of Events (Appendix A)
p) Sections 9.1.1 and 9.3.2 Adverse Events – updated to include monitoring for AEs suggesting bladder dysfunction
q) Appendix A Schedule of Events
    1. Added Visit names (ie Visit 1, Visit 2, Visit 3, etc) for referencing each visit to help in maintaining blind
    2. Allow for extending the Run-in Period by up to 3 days
r) Appendix C – add collection of cytokine/chemokines sample as part of biomarkers

s) Appendix D
    1. Corrected number of PK samples to be collected on Day 1 (11 not 9), Day 2 (11 not 10), and Week 6 (12 not 10) visit; total PK blood samples (35 not 30); and total volume of PK blood draw (140 mL not 120 mL)
    2. Added samples for cytokine/chemokine analysis (5 samples x 4 mL each = 20 mL total)

t) Add Appendix M for Numerical Rating Scale (NRS)