Statistical Analysis Plan

A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of NYX-2925 in Subjects with Neuropathic Pain Associated with Diabetic Peripheral Neuropathy -- Protocol Number: NYX-2925-2008

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Protocol Number: *NYX-2925-2008*

Protocol Version: *8.0, Amendment 7, dated 25-Jun-2021*

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1 INTRODUCTION

This document details the planned statistical analyses for Aptinyx Inc., protocol NYX-2925-2008 study titled "A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of NYX-2925 in Subjects with Diabetic Peripheral Neuropathy".

The proposed analyses are based on Protocol Amendment 7, dated 25-Jun-2021.

This is a 13- to 16-week double-blind study that includes a 1- to 4-week Screening Period and a 12-week, double-blind, randomized, placebo-controlled Treatment Period in which subjects will take one capsule of study drug once daily by mouth. Rescue medication, which consists of 500 mg tablets of acetaminophen, is also provided by sponsor. Subjects will be instructed to take one to two 500 mg tablets every 6 hours as needed up to 4 tablets total for DPN related pain, not to exceed 2 g/day. A safety follow-up call is also to be made to the subjects within 10 days and then approximately 30 days after week 12/ final visit to assess for any AE/SAE closure and any newly reported SAEs.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objectives of this study are:

- To evaluate the efficacy of NYX-2925 50 mg QD versus placebo in treating neuropathic pain associated with diabetic peripheral neuropathy.
- To assess the safety and tolerability of NYX-2925 50 mg QD.

2.2 Secondary Objectives

The secondary objective of this study is to assess effects of NYX-2925 50 mg QD versus placebo on pain characteristics, sleep interference, psychological state, and global improvement.

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3 ENDPOINTS

3.1 Primary Endpoint

The primary efficacy endpoint is the change from baseline to Week 12 in the weekly mean Numeric Rating Scale (NRS) score assessing average pain intensity related to DPN in the past 24 hours.

3.2 Secondary Endpoints

The secondary efficacy endpoints are:

- Change from baseline in the weekly mean of the Daily Sleep Interference Scale (DSIS) scores at Week 12.
- Percentage of subjects 'much improved' or 'very much improved' on Patient Global Impression of Change (PGI-C) at Week 12.
- Percentage of subjects achieving ≥30% pain reduction from baseline in the weekly mean NRS average pain intensity related to DPN at Week 12.
- Percentage of subjects achieving ≥50% reduction from baseline in the weekly mean NRS average pain intensity related to DPN at Week 12.
- Change from baseline to Week 12 in Norfolk Quality of Life Questionnaire – Diabetic Neuropathy (QOL-DN) score.
- Use of rescue medication, including the proportion of subjects using rescue medication, the frequency and amount used.
- Cumulative response (percent reduction from baseline) in the weekly mean NRS average pain intensity at Week 12.
- Change from baseline in the weekly mean Numerical Rating Scale (NRS) score assessing average pain intensity related to DPN at each week from Week 1 through Week 12.

3.3 Other Efficacy Endpoints

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3.4 Safety Endpoints

The safety endpoints will include adverse events (AE), serious adverse events (SAE), discontinuation due to AE and the S-STS.

4 SAMPLE SIZE

The planned sample size is a total of 204 randomized subjects. This will provide approximately 80% power to detect a difference in means of 0.73 assuming that the common standard deviation is 1.7 (and accounting for 15% drop-out rate), using two-sided statistical testing with an overall Type I error rate of 0.05.

5 RANDOMIZATION

Pain scores reported by subjects during the Screening Period will be evaluated by the Interactive response technology (IRT) system for raw score and for variability among scores after transmission of pain scores from the handheld devices to determine randomization eligibility. Subjects whose mean of the daily average pain intensity score during the preceding seven (7) days is within the protocol-defined algorithm and whose compliance with daily diary completion is adequate will be eligible for randomization. The absolute pain scores and variability among scores, as well as the actual percentage required for diary compliance, will be masked to investigators and subjects. Subject eligibility for randomization into the study based on these variables will be communicated to the investigator via the IRT system. The IRT system will notify the site if the subject is "Eligible" or "Not eligible." No other information will be provided.

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Eligible subjects will be randomized to receive either NYX-2925 50 mg or placebo daily in a 1:1 allocation.

6 PLANNED ANALYSES

The final Clinical Study Report (CSR) may contain additional tables or statistical tests if warranted by the data obtained. The justification for any such additional analyses will be fully documented in the final CSR.

6.1 Analysis Populations

Subjects excluded from the analysis populations and the reason for their exclusion will be listed in Appendix 16.2 of the CSR.

6.1.1 Screened Population

The Screened Population includes all subjects who are screened.

6.1.2 Randomized Population

The Randomized Population includes all subjects who were assigned a randomization number in IRT.

6.1.3 Safety Population

The Safety Population includes all subjects who received at least one dose of study drug. For safety analyses, subjects will be grouped based upon the treatment received. In the event that a subject receives both treatments (NYX-2925 and placebo), the subject will be grouped under NYX-2925.

6.1.4 Modified Intent-to-Treat Population

The Modified Intent-to-Treat (mITT) Population includes all subjects in the Safety Population with at least one post-baseline assessment of the pain intensity NRS. Efficacy analyses for the mITT Population will have subjects grouped based on their planned treatment. All efficacy analyses will be performed on the mITT Population.

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6.2 Derived Data

This section describes the derivations required for statistical analysis. Unless otherwise stated, variables derived in the source data will not be re-calculated.

6.2.1 Race

Where more than one race category has been selected for a subject, these race categories will be combined into a single category labeled "Multiple" in the summary tables. The listings will reflect the original selected categories.

6.2.2 Baseline

Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the subject receives the first dose of study drug.

For endpoints in which the weekly mean is being utilized, baseline is defined as the average of the available assessments on the last 7 days prior to the first dose of study drug (study days -7 to -1).

6.2.3 Duration / Study Day / Time

Study day will be calculated as the number of days from first dose of study drug.

- date of event – date of first dose of study drug + 1, for events on or after first dose
- date of event – date of first dose of study drug, for events before first dose

6.2.4 Conventions for Missing and Partial Dates

All rules explained below for partial / missing dates will be followed unless contradicted by any other data recorded on the electronic Case Report Form (eCRF).

All dates presented in the individual subject listings will be as recorded on the eCRF (i.e., not completed as per the below rules).

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6.2.5 Missing / Partial Start / Stop Date of Adverse Events (AE) and Concomitant Medications

Missing and partial start and stop date will be imputed for analysis purposes for Adverse Events (including Medical History) and Concomitant Medications as follows.

Partial or missing stop date will be imputed as follows:

- If the stop date is completely missing and the event has resolved, or the subject has stopped taking the concomitant medication, the stop date will be imputed as the date of the subject's last clinic visit in the study.
- If only the year is known, the stop date will be imputed as "31-Dec" of that year or as the date of the subject's last clinic visit in the study if in the same year.
- If the month and year are known, the stop date will be imputed as the last day of that month unless the stop date corresponds to the same month as the subject's last clinic visit in which case the date of subject's last clinic visit in the study will be used instead.

Missing start date will be imputed as follows:

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, the start date will be imputed as the date of the first dose of study drug.
- If the stop date occurs before the start of study drug, the start date of the event / concomitant medication will be imputed as the subject's screening date or the stop date of the event / concomitant medication whichever the earlier.

Partial start date (year present, but month and day missing)

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, and the year is the same as the year of first dosing the start date will be imputed as the date of the first dose of study drug. If the year is different from the year of first dosing "01-Jan" will be used.
- If the stop date occurs before the start of study drug, the start date of the event / concomitant medication will be imputed as the "01-Jan" of the same year.

Partial start date (month and year present, but day missing)

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, the start date will be imputed as the first day of the same month and

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year unless this partial start date is in same month as the first dose of study drug in which case the date of first dose of study drug will be used.

- If the stop date occurs before the start of study drug, the start date will be imputed as the first day of the month and year of the partial stop date.

6.2.6 Missing Last Dates of Study Drug Dosing

If the date of last dose of study drug is completely missing, then the date of last dose of study drug will be taken for analysis purposes as the date when the subject would have run out of study drug assuming full compliance from the date the study drug was last dispensed, or the date of subject's last clinic visit in the study (if study drug is returned) or early withdrawal or death whichever the earlier.

If only the month and year of the last dose was recorded, then the date of last dosing will be taken for analysis purposes as the date the subject would have run out of study drug assuming full compliance from the date the study drug was last dispensed, the last day of the month of the recorded last dose or the date of subject's last clinic visit in the study (if study drug is returned) or early withdrawal or death whichever the earlier.

6.2.7 Prior Analgesic Use

Subjects will be classified as those who have previously taken gabapentin, pregabalin or duloxetine versus those who have not taken any of these, based on prior medications reported.

6.2.8 Exposure to Study Drug

Exposure to study drug (days) will be calculated as follows:

$$(Date\ of\ last\ dose\ of\ study\ drug\ -Date\ of\ first\ dose\ of\ study\ drug\ )+1$$

The exposure calculation will not take into account breaks in therapy.

6.2.9 Treatment Compliance

Treatment compliance will be calculated per visit interval (Visit 2 to Visit 4, Visit 4 to Visit 5, and Visit 5 to Visit 6) as follows:

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$$\frac{Total\ number\ of\ capsules\ dispensed - Total\ number\ of\ capsules\ returned}{(Number\ of\ days\ within\ the\ visit\ interval)} \times 100$$

Total number of capsules dispensed will be obtained as below:

- Visit 2 to Visit 4: the total number of capsules dispensed at Visit 2
- Visit 4 to Visit 5: the total number of capsules dispensed at Visit 4
- Visit 5 to Visit 6: the total number of capsules dispensed at Visit 5

Total number of capsules returned will be obtained as below:

- Visit 2 to Visit 4: the total number of capsules returned at Visit 4
- Visit 4 to Visit 5: the total number of capsules returned at Visit 5
- Visit 5 to Visit 6: the total number of capsules returned at Visit 6

The number of days within the visit interval is obtained as follows:

- Visit 2 to Visit 4: (Date of Visit 4 – Date of first dose of study drug) + 1
- Visit 4 to Visit 5: (Date of Visit 5 – Date of Visit 4)
- Visit 5 to Visit 6: (Date of Visit 6 – Date of Visit 5)

The number and percentage of subjects with compliance ≥80% will also be provided by treatment group for each interval.

6.2.10 Inexact Values

In the case where a laboratory parameter has result recorded as "> x", "≥ x", "< x" or "≤ x", a value of x will be taken for analysis purposes.

6.2.11 Electrocardiogram Data

For electrocardiogram (ECG) data recorded on continuous scales, if more than one value (for instance, triplicate recordings) is recorded at a time point (i.e., date), the mean value rounded to the integer will be presented. in the event that one reading is missing, the average of the available two readings will be used for the analysis. Furthermore, if only one reading is available, this reading will be used for the analysis.

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For overall interpretation if more than one interpretation is recorded, the most severe (worst case) interpretation will be presented.

6.2.12 Early Withdrawal Assessments

For the analysis, assessments performed at early withdrawal visits for the subjects who discontinued will be mapped to the closest visit, using midpoints between visits to window the early withdrawal. If the early withdrawal assessment is mapped to a visit where a scheduled assessment is already present, the scheduled assessment will take precedence, and the early withdrawal assessment will be disregarded (and listed only).

Note that the windowing will be specific to the measure, per the below table. For example, PGI-C is collected at Weeks 4, 8, and 12 and thus the early withdrawal assessment for PGI-C would be windowed with Day 2 to Day 42 as Week 4, Day 43 to Day 70 as Week 8, and Day 71+ as Week 12. The BPI-DPN is collected at Weeks 4 and 12. Thus, early withdrawal assessments would be windowed with Day 2 to Day 56 as Week 4, and Day 56+ as Week 12.

Assessment(s)	Timing of Early Withdrawal Assessment	Mapped Visit
PCS, Physical Exam	Day 2+	Week 12
BPI-DPN, Norfolk QoL-DN	Day 2 to Day 56	Week 4
	Day 57+	Week 12
ECG	Day 2 to Day 70	Week 8
	Day 71+	Week 12
Vital signs, Laboratory samples, PGI-C	Day 2 to Day 42	Week 4
	Day 43 to Day 70	Week 8
	Day 71+	Week 12
Sheehan STS	Day 2 to Day 21	Week 2
	Day 22 to Day 42	Week 4
	Day 43 to Day 70	Week 8
	Day 71+	Week 12

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6.2.13 Unscheduled Visits

Unscheduled visits will be handled in an identical manner as described in Section 6.2.12. If this results in multiple records for a given visit, then the scheduled visit will take highest precedence, followed by early withdrawal visits, and unscheduled visits last.

6.2.14 Change from Baseline

Change from baseline in absolute terms is defined as the baseline value subtracted from the post-baseline values. This calculation method will be used as part of the calculation for percentage change from baseline calculations.

$$Change\ from\ Baseline\ =\ Post\text{-}baseline\ Value\ -\ Baseline\ Value$$

6.2.15 Percent Change from Baseline

Percent change from baseline will be calculated as change from baseline multiplied by 100 then divided by the baseline value.

$$Percent\ Change\ from\ Baseline\ =\ \frac{Change\ from\ Baseline\ \times 100}{Baseline\ Value}$$

6.2.16 Pooled Sites

The study protocol indicates that study site will be included as factor in statistical models . It was further indicated that the study can include up to 37 study sites in the United States. It is likely that some of these sites will have small numbers of subjects included in the mITT population, which could lead to convergence issues, unreliable treatment effect estimates and p-values. Thus, in the event that there are study sites with fewer than 6 subjects included in the mITT population, these sites will be pooled together to form a single site, such that the pooled sites will have a minimum of 6 subjects included in the mITT. The resulting pooled sites (referred to as "site" from here on) will be used in the analyses.

6.2.17 Numerical Rating Scale

The Numerical Rating Scale (NRS) is a unidimensional, segmented numeric scale in which a respondent selects a whole number (0-10 integers) that best reflects the intensity of the pain. The

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format is a horizontal bar or line that is anchored by terms describing pain levels where a score of 0 represents "no pain" and a score of 10 represents "worst pain imaginable". Subjects will report pain intensity during the past 24 hours daily at bedtime in the handheld diary.

NRS score will be obtained for:

- Average pain intensity related to DPN in the past 24 hours
- Average pain intensity upon walking in the past 24 hours
- Worst pain intensity related to DPN in the past 24 hours

6.2.17.1 Baseline Mean NRS Score

The baseline mean NRS score is defined as the average of the NRS scores on the last 7 days prior to the first dose of study drug (Study days -7 to -1). A minimum of 5 non-missing NRS scores out of the 7 days is required for the baseline mean NRS score.

$$Baseline\ NRS\ =\ Sum\ of\ daily\ NRS\ scores\ (over\ 7\ days)/\ Number\ of\ available\ diaries$$

6.2.17.2 Post-Baseline Weekly Mean NRS Scores

Weekly Mean NRS Scores for Week 12 (and prior weeks) will be obtained based on the subject's actual Week 12 visit date. If the subject's Week 12 visit date is within Day 80 to Day 88, then the 7th NRS score for Week 12 will be the corresponding NRS score on the day before the subject's Week 12 visit date, and the 6th to 1st NRS score for Week 12 will be obtained backwards from this. Thus, the corresponding NRS scores on the last 7 days prior to Week 12 actual visit date will be used for Week 12. Consequently, the Week 11 NRS scores will be obtained by counting 7 days backwards from the 1st NRS score for Week 12, Week 10 NRS scores will be obtained by counting 7 days backwards from the 1st NRS score for Week 11 and continuing up to Week 1. If the subject's actual Week 12 visit date is beyond Day 88, then the corresponding NRS score on the day before Day 88 (i.e., Day 87) will be used as the 7th NRS score for Week 12, and the 6th to 1st NRS score will be obtained backwards from this and continuing for each week from Week 11 to Week 1. Meanwhile, if the subject's actual Week 12 visit date is earlier than Day 80, then no Week 12 data will be identified.

Timing of Week 12 Visit	Reference Day (NRS)
Day 80 to Day 88	Count backwards from day before Week 12 visit (Week 12 study day -1)

[redacted]

[redacted]

Day 89+	Count backwards from Day 87 only
Earlier than Day 80	No Week 12 data identified

For subjects that withdraw early or have missing data such that they do not have any data that would fall into the Week 12 windowing, their last non-missing diary day will serve as the anchor; weeks will be counted backwards in 7-day intervals from the last day. For the week ending with this anchor day, study week will be assigned such that the majority of days fall in the nominal week. For example, Week 11 is nominally day 71-77; if a subject's last value is on day 74, the majority of the resulting 7-day window working backwards would be in "Week 11", so their last week would be analyzed as "Week 11" and the subsequent intervals assigned descending weeks working backwards. The following table shows how the last interval will be assigned based on its last day.

Timing of Last Non-Missing Diary	**Assigned Week** (from which to count backwards)
Day 1 to Day 10	Week 1
Day 11 to Day 17	Week 2
Day 18 to Day 24	Week 3
Day 25 to Day 31	Week 4
Day 32 to Day 38	Week 5
Day 39 to Day 45	Week 6
Day 46 to Day 52	Week 7
Day 53 to Day 59	Week 8
Day 60 to Day 66	Week 9
Day 67 to Day 73	Week 10
Day 74 to Day 80	Week 11
NA	Week 12

Change from baseline and percent change from baseline will be calculated by subtracting baseline mean score from the post-baseline weekly mean scores, as defined in Sections 6.2.14 and 6.2.15.

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6.2.17.3 Definition of ≥30% and ≥50% Responder

Subjects who achieve a percent reduction in NRS score relating to 'Average pain intensity related to DPN in the past 24 hours' of ≥30% (programmatically, where the change from baseline value is ≤ –30) at Week 12 will be classified as responders, and non-responders otherwise.

Similarly, subjects who achieve a percent reduction in NRS score relating to 'Average pain intensity related to DPN in the past 24 hours' of ≥50% (programmatically, where the change from baseline value is ≤ –50) at Week 12 will be classified as responders, and non-responders otherwise.

Subjects with missing weekly mean NRS score relating to 'Average pain intensity related to DPN in the past 24 hours' at Week 12 will be classified as non-responders.

6.2.17.4 Time to First ≥30% and ≥50% Reduction

The time to first ≥30% (and ≥50%) reduction in NRS score relating to 'Average pain intensity related to DPN in the past 24 hours' will be identified as follows.

A moving average of the NRS average pain intensity will be calculated, that is, average NRS score for moving 7-day intervals from Day 1 to Day 7, from Day 2 to Day 8, from Day 3 to Day 9, and so on, up to the final interval of Day 78 to Day 84.

Percentage reduction from Baseline Mean NRS (as defined in Section 6.2.17.1) for each moving average interval will be calculated using the percentage change from baseline method described in Section 6.2.15.

The first moving average interval that yields a reduction from baseline of ≥30% (and ≥50%) will be identified and the last day of this block of 7 days will be the date of first ≥30% (and ≥50%) reduction.

Subjects who failed to achieve the target reduction (≥30% and ≥50%) will be censored on the day of the last non-missing average pain intensity score, or the Week 12 visit date (whichever is later), for that subject.

Subjects who discontinued the study prior to Week 12 and who failed to achieve the target reduction (≥30% and ≥50%) while on the study will be censored at the time of discontinuation.

Time to the first ≥30% (and ≥50%) reduction (days) will subsequently be obtained as follows:

Date of first ≥30% (and ≥50%) reduction – date of dosing of study drug

[redacted]

[redacted]

6.2.18 Daily Sleep Interference Scale

The Daily Sleep Interference Scale (DSIS) is a single-item measure with 11-point response scale (0-10; where 0 corresponds to "did not interfere with sleep" and 10 corresponds to "completely interfered with sleep/unable to sleep due to pain) that quantify sleep interference due to pain. The subjects complete this questionnaire daily upon awakening each morning.

Baseline mean score will be obtained as described in Section 6.2.2. Weekly mean DSIS data will be obtained for Week 12 data (and prior weeks) based on the subjects actual Week 12 visit date.

If the subject's Week 12 visit date is within Day 80 to Day 88, then data on the actual Week 12 visit date up to 6 days prior to this date will be the corresponding data for Week 12 visit date. Consequently, the Week 11 data will be obtained by counting 7 days backwards from the 1st day of Week 12, Week 10 NRS scores will be obtained by counting 7 days backwards from the 1st day of Week 11, and the process continue up to Week 1. If the subject's actual Week 12 visit date is beyond Day 88, then the corresponding data from Day 82 to Day 88, inclusive, will be the Week 12 data. Similar process as described previously will be used to obtain the data for each week from Week 11 up to Week 1. Meanwhile, if the subject's actual Week 12 visit date is earlier than Day 80, then no Week 12 data will be identified.

Timing of Week 12 Visit	Reference Day (DSIS or Rescue Medication)
Day 80 to Day 88	Count backwards from day of Week 12 visit
Day 89+	Count backwards from Day 88 only
Earlier than Day 80	No Week 12 data identified

For subjects that withdraw early or have missing data such that they do not have any data that would fall into the Week 12 windowing, their last non-missing diary day will serve as the anchor, as described in Section 6.2.17.2.

6.2.19 Rescue Medication

Use of rescue medication (number of tablets taken) is recorded daily at bedtime in the handheld diary. Weeks will be identified and assigned using the same method as described in Section 6.2.17.2 for NRS data. For each week, the total number of tablets reported per week will be summed and percentage of rescue-free days per week will be obtained.

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A subject using rescue medication is defined as any subject who recorded one or more tablets in the daily diary at any time after the first dose of study drug.

Percentage of rescue-free days per week will be obtained by taking the number of days where rescue medication was answered 'No' in the daily diary and divided by the number of non-missing diary entries for the week.

Weekly dosage of acetaminophen (mg) will be calculated using the total number of tablets taken for each week multiplied by 500 mg.

6.2.20 Patient Global Impression of Change

Patient Global Impression of Change (PGI-C) is a 7-point scale (1 to 7; where 1 corresponds to 'very much improved, 4 is 'no change', and 7 is 'very much worse') that captures the subjects' impression of their overall change since the beginning of the study to specific time points during the study.

For the analysis, subjects will be classified as either responders, that is, a PGIC response of 1 ('very much improved') or 2 ('much improved'), or non-responders, that is, all other PGIC responses (recorded as 3, 4, 5, 6 and 7) at Week 12. Subjects will be classified as non-responders if their PGIC assessments at Week 12 are missing.

6.2.21 Norfolk Quality of Life Questionnaire – Diabetic Neuropathy

The Norfolk Quality of Life Questionnaire – Diabetic Neuropathy (QOL-DN) is a 47-item subject-reported questionnaire designed to measure the relationship between symptomatic diabetic neuropathy and quality of life from the perspective of the subject. It consists of two parts: 1. questions related to symptoms experienced by the patient which has five possible responses ("feet", "leg", "hands", "arms", and "none") and 2. questions related to the impact of patients' neuropathy on activities of daily life in which the responses are in a 5-point Likert scale (0-4; where 0 corresponds to "not a problem" and 4 corresponds to "severe problem"). Further, the questionnaire has five domains: activities of daily living, symptoms, small fiber neuropathy, large fiber neuropathy, and autonomic neuropathy. The QOL-DN total score is calculated as the sum of all the domain scores, which are obtained as follows:

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response to the question is "none" then the item score is 0, and 1 otherwise. The symptom domain score is obtained as the sum of the item scores of the seven symptoms questions plus the response to the question "*In the past 4 weeks, has the touch of bed sheets, clothes, or wearing shoes bothered you?*". Thus, the symptoms domain score is the sum of eight questions in total with a minimum domain score of 0 and maximum domain score of 32.

Activities of daily living: The activities of daily living domain score is obtained by summing the responses to questions 12, 22, 23, 25, and 26 (see below). Thus, the minimum domain score is 0 and maximum domain score is 20.

Question 12: in *the past 4 weeks, have you had difficulty doing fine movements with your fingers, like buttoning your clothes, turning pages in a book, picking up coins from a table?*

Question 22: in *the past 4 weeks, how much difficulty have you had performing the following activities: Bathing/Showering?*

Question 23: *in the past 4 weeks, how much difficulty have you had performing the following activities: Dressing?*

Question 25: in *the past 4 weeks, how much difficulty have you had performing the following activities: Getting on or off the toilet?*

Question 26: *in the past 4 weeks, how much difficulty have you had performing the following activities: Using eating utensils?*

Small fiber neuropathy: The small fiber neuropathy domain score is obtained by summing the responses to questions 10, 16, 17, and 18 (see below). Thus, the minimum domain score is 0 and maximum domain score is 16.

Question 10: in *the past 4 weeks, have your burned or injured yourself and been unable to feel it?*

Question 16: in *the past 4 weeks, have you been unable to feel your feet when walking?*

Question 17: in *the past 4 weeks, have you been unable to tell hot from cold water with your hands?*

Question 18: *in the past 4 weeks, have you been unable to tell hot from cold water with your feet?*

Large fiber neuropathy: The large fiber neuropathy domain score is obtained by summing the responses to questions 8, 11, 13, 14, 15, 24, 27, 28, 29, 30, 33, 34, and 35 (see below) plus the responses to the following questions with the corresponding item scores. Thus, the large fiber neuropathy domain score is the sum of 15 questions in total with a minimum domain score of -4 and maximum domain score of 56.

[redacted]

- "*In general, would you say your health now is:*"
  Response & item score: Excellent = -2, Very Good = -1, Good = 0, Fair = 1, and Poor = 2
- "*Compared with 3 months ago, how would you rate your health in general now?*"
  Response & item score: Much Better = -2, Somewhat Better = -1, About the Same = 0, Somewhat Worse = 1, Much Worse = 2

Question 8: in *the past 4 weeks, has pain kept you awake or woken you at night?*
Question 11: in *the past 4 weeks, have any symptoms kept you from doing your usual activities during the day?*
Question 13: *in the past 4 weeks, have you felt unsteady on your feet when you walk?*
Question 14: in *the past 4 weeks, have you had any problem getting out of a chair without pushing with your hands?*
Question 15: in *the past 4 weeks, have you had a problem walking down stairs?*
Question 24: in *the past 4 weeks, how much difficulty have you had performing the following activities: Walking?*
Question 27: in *the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical and emotional health: Cut down on the amount of time you spent on work or other activities?*
Question 28: in *the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical and emotional health: Accomplished less than you would like?*
Question 29: in *the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical and emotional health: Were limited in the kind of work or other activities you could perform?*
Question 30: in *the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical and emotional health: Had difficulty performing the work/other activities (it took extra effort)?*
Question 33: in *the past 4 weeks, to what extent has your physical health interfered with your normal social activities with family, friends, neighbors, or groups?*
Question 34: *in the past 4 weeks, how much did pain interfere with your normal work (including work both outside the home and housework)?*
Question 35: in *the past 4 weeks, how much did weakness or shakiness interfere with your normal work (including work both outside the home and housework)?*

[redacted]

Autonomic neuropathy: The autonomic neuropathy domain score is obtained by summing the responses to questions 19, 20, and 21 (see below). Thus, the minimum domain score is 0 and maximum domain score is 12.

Question 19: *in the past 4 weeks, have you had a problem with vomiting, particularly after meals (but not due to flu or other illness)?*

Question 20: in *the past 4 weeks, have you had a problem with diarrhea and/or loss of bowel control?*

Question 21: in *the past 4 weeks, have you had a problem with fainting or dizziness when you stand?*

6.2.22 Brief Pain Inventory for Diabetic Peripheral Neuropathy

The Brief Pain Inventory for Diabetic Peripheral Neuropathy (BPI-DPN) is a patient-completed numerical rating scale that assesses the severity of pain (Severity scale), it's impact on daily functioning (Interference scale), and other aspects of pain (location of pain, relief from medications, etc.). The Severity scale which consists of 4 items (Worst, Least, Average, Pain now) uses a 0 to 10 numeric rating scale for each item where 0 corresponds to "no pain" and 10 corresponds to "pain as bad as you can imagine". Moreover, the Interference scale which consists of 7 items (General Activity, Mood, Walking Ability, Normal Work, Relations with Others, Sleep, Enjoyment of Life) also uses a 0 to 10 numeric rating scale for each item where 0 corresponds to "does not interfere" and 10 corresponds to "completely interferes".

The Pain Severity index, which is the average of all items of the Severity scale, will be obtained as long as all items in the Severity scale have a reported score. Otherwise, it will be set to missing.

Similarly, the Pain Interference index which is the average of all items of the Interference scale, will be obtained as long as at least 4 items in the Interference scale have a reported score. Otherwise, it will be set to missing. These are the composite scores of interests. No BPI-DPN total score will be calculated

6.2.23 Pain Catastrophizing Scale

The Pain Catastrophizing Scale (PCS) is a comprehensive evaluation instrument that encompasses different perspectives on catastrophizing and assesses the state of mind of patients in pain. The PCS has 13 items which are statements describing different thoughts or feelings that may be

[redacted]

[redacted]

associated with pain. Each item has a response on a 5-point Likert scale (0-4; where 0 corresponds to "not at all" and 4 corresponds to "all the time") which reflects the degree of the subject's thoughts and feelings when experiencing pain.

The PCS total score (which ranges from 0 to 52) is calculated by summing responses to all 13 items. PCS subscale scores can be obtained as follows: Rumination (sum of items 8, 9, 10, 11); Magnification (sum of items 6, 7, 13); Helplessness (sum of items 1, 2, 3, 4, 5, 12).

For this study, item 7 was not recorded, therefore a modified PCS score (sum of the 12 remaining items, ranging from 0-48) will be calculated. The Rumination and Helplessness subscale scores will be calculated as described; however, the Magnification subscale score will be omitted from the analysis.

Pain Catastrophizing Scale (PCS) – 13 Items

- Item 1: Worry Whether the Pain Will End
- Item 2: Feel I Can't Go
- Item 3: Terrible- Think Never Get Better
- Item 4: Pain Overwhelms Me
- Item 5: Can't Stand it Anymore
- Item 6: Afraid the Pain Will Get Worse
- ~~Item 7: Thinking of other Painful Events~~ [Not Recorded for This Study]
- Item 8: Anxiously Want Pain to Go Away
- Item 9: Can't Seem to Keep Out of Mind
- Item 10: Keep Thinking How Much It Hurts
- Item 11: Keep Thinking- Want Pain to Stop
- Item 12: Nothing Reduces Intensity of Pain
- Item 13: Wonder Something Serious Happen

6.2.24 Sheehan-Suicidality Tracking Scale

The standard version of the Sheehan-Suicidality Tracking Scale (S-STS) is a 16-item scale that assesses the seriousness of suicidality phenomena on a Likert-type scale (0 to 4; where 0 corresponds to "not at all" and 4 corresponds to "extremely"). It also assesses the frequency of key phenomena and the overall time spent in suicidality. The total S-STS score is obtained by summing the responses to:

[redacted]

[redacted]

- question 1a (only if the answer to question 1b: *did you intend to die as a result of any accident?* is "Yes")
- questions 2 to 11
- max of responses to question 12 or any row of question 16
- max of responses to question 14 or any row of question 15

Question 1a: *how seriously did you plan or intend to hurt yourself in any accident, either by not avoiding a risk or by causing the accident on purpose?*

Question 2: *think (even momentarily) that you would be better off dead, need to be dead or wish you were dead?*

Question 3: *think (even momentarily) about harming or hurting or injuring yourself – with at least some intent or awareness that you might die as a result – or think about suicide (killing yourself)?*

Question 4: *have a voice or voices telling you to kill yourself or have dreams with any suicidal content?*

Question 5: *have any suicide method in mind (i.e., how)?*

Question 6: *have any suicide means in mind (i.e., with what)?*

Question 7: *have any place in mind to attempt suicide (i.e., where)?*

Question 8: *have any date / timeframe in mind to attempt suicide (i.e., when)?*

Question 9: *intend to act on thoughts of killing yourself?*

Question 10: *intend to die as a result of a suicidal act?*

Question 11: *feel the need or impulse to kill yourself or to plan to kill yourself sooner rather than later?*

Question 12: *take active steps to prepare for a suicide attempt in which you expected or intended to die (include anything done or purposely not done that put you closer to making a suicide attempt)?*

Question 14: *attempt suicide (try to kill yourself)?*

Question 15: *Since your last visit, how many times did you attempt suicide?*

[redacted]

[redacted]

Question 16: *Since your last visit, how many times did you take active steps to prepare for a suicide attempt in which you expected or intended to die (include anything done or purposely not done that put you closer to making a suicide attempt)?*

6.2.25 Liver Function Abnormalities

Any subject meeting the following criteria will be identified and results will be listed separately for these subjects:

- ALT or AST >3xULN or Bilirubin >2xULN

Where ALT = Alanine Aminotransferase, AST = Aspartate Aminotransferase, and ULN = Upper Limits of Normal.

6.3 Conventions

6.3.1 Medical Coding

Adverse events and medical history will be coded using the Medical Dictionary of Regulated Activities (MedDRA) Version 24.1 (or higher). Conditions will be assigned to a primary system organ class (SOC) and preferred term (PT) based on the Investigator-reported verbatim term.

Any medications taken (other than study drug) will be coded using the World Health Organization Drug Dictionary (WHO Drug) September 2021 Version (or higher). Medications (both prior and concomitant) will be assigned to an Anatomical Therapeutic Chemical (ATC) Level 3 drug classification and Preferred Name based on the medication name reported on the eCRF.

6.3.2 Data Handling

All clinical data programming will be performed using SAS® statistical software package (Statistical Analysis System, Version 9.4 or higher)**Error! Reference source not found.** and based on Clinical Data Interchange Standards Consortium (CDISC) data standards.

Study Data Tabulation Model (SDTM) programming will follow SDTM version 1.7 together with SDTM implementation guide 3.3. Analytical Data Model (ADaM) programming will follow ADaM implementation guide 1.1. Specifications for SDTM and ADaM datasets are described in a separate document.

[redacted]

[redacted]

6.3.3 Validation Methods

All programming of datasets and outputs will be validated by independent programming (IP) of values, programmatic comparison and manual review of format compared to the SAP and agreed shell template. Figures will be validated by manual review of format and visual inspection of graphical display compared to tabulated data. Independent programming by a Statistician (Stat IP) will be performed for all analyses relating to the primary endpoint.

6.3.4 Descriptive Statistics

Continuous variables will be summarized by the number of non-missing observations, mean, median, standard deviation, and minimum and maximum.

Categorical variables will be summarized by presenting the frequency and percent. Percentages will be based on the number of non-missing observations or the subject population unless otherwise specified. For each variable, all categories will be shown. Zero frequencies (but not the percent) within a category will be presented.

Incidences of adverse events, medical history and concomitant medications will be reported at the subject level. Subjects can only be counted once within each PT and SOC under the highest severity and most related. Percentages will be calculated using the number of subjects in the treatment group for the Safety Population.

6.3.5 Decimal Places

Decimal places for derived data described in Section 6.2 will be determined by the scale of measurement unless otherwise stated. No decimal places will be displayed if the smallest calculated value is ≥ 100; 1 decimal place will be displayed when the smallest value is within the interval (10, 100), with 10 being inclusive; 2 decimal places will be displayed when the smallest value is within (1, 10), with 1 being inclusive; and so on for even smaller scales of measurement.

Derived data where it is known in advance the result will be an integer for example day, month, year, number of days and total scores (for rating scales) will be presented with zero decimal places.

For descriptive (summary) statistics, n will be reported as a whole number. Means, medians, and percentiles will be displayed to one more decimal place than the data**,** dispersion statistics (e.g., standard deviation) will have two more decimal places, and the minimum and maximum will be

[redacted]

[redacted]

displayed to the same number of decimal places as reported in the raw data. Percentages will be displayed with one decimal place. All data presented in the individual subject listings will be as recorded on the eCRF.

Individual weekly mean values will be calculated to one decimal place and summary statistics presented per the above quoted convention.

LS means and 95% CIs will be quoted to 2 decimal places. P-values will be quoted to 3 decimal places and p-values < 0.001 will be presented as p<0.001.

6.3.6 Data Displays

All clinical data tabulations, figures and listings will be generated as individual Rich Text Format (.rtf) files using SAS (Version 9.4 or higher)[1]. Data summaries, statistical analyses and graphical analyses will be reported within Section 14 of the CSR and individual subject data listings within Appendix 16.2 of the CSR. Specifications (shells) for Tables, Figures and Listings will be provided as a separate document.

Subject disposition, baseline characteristics, demographic data, treatment exposure, compliance, medical history, concomitant medication, and adverse event data will be presented by treatment group and overall.

Other safety and efficacy data will be presented by treatment group only.

Treatment group labels will be displayed as follows:

NYX-2925 50 mg	Placebo
(N=XX)	(N=XX)

Listings will be sorted in the following order: treatment group, subject, parameter, and visit unless otherwise stated. All data will be listed. For some listings, subjects who were not randomized will be presented but will be displayed after the randomized treatment groups.

6.4 Subject Disposition

Subject disposition will be summarized as follows:

[redacted]

[redacted]

- The number of subjects, who entered the study, were randomized and who are in each analysis population will be summarized by treatment group and overall.
- *The number of subjects who failed screening and the reasons for failure will be tabulated for all subjects.
- The number of subjects who were not randomized and the reasons subjects were not randomized will be tabulated for all subjects.
- The number of early withdrawals and the reasons for withdrawal will be tabulated by treatment group and overall.
- The number of subjects who completed the study will also be tabulated by treatment group and overall.

*For participants who were re-screened, reason for screen failure will be taken from the most recent screening attempt. Data from both attempts will be listed.

6.5 Protocol Deviations

Protocol deviation categories will be tabulated by treatment group and classification (Major, Minor) for the Safety Population. Additionally, COVID-19 related protocol deviations will be identified. A listing of protocol deviations will be provided within Appendix 16.2 of the CSR.

6.6 Baseline Comparability

Comparability of treatment groups with respect to subject demographics and baseline characteristics will be assessed in a descriptive manner.

Standard continuous or categorical variable summaries will be presented by treatment group and overall, for the following variables, for the Safety Population.

Demographic Data

- Age at Informed Consent (years)
- Sex (Male/Female)
- Ethnicity
- Race, where more than one race is selected the participant will be presented under the 'Multiple races' category in the summary but each selected race will be identified in the listing.

[redacted]

[redacted]

Baseline Characteristics

- Weight at Screening (kg)
- Height at Screening (cm)
- BMI at Screening (kg/m^2)
- Childbearing Potential (for female subjects only)

Clinical Characteristics

- Discontinuation of prior analgesic medications at Baseline (Yes/No/NA)
- Duration of DPN at Baseline (years)
- Duration of Painful DPN at Baseline (years)
- Patient Global Impression of DPN Severity
- Neurological Examination at Baseline (Normal/Abnormal, Not Clinically Significant [NCS], Abnormal, Clinically Significant [CS])

6.7 Medical History

Separate tabulations of prior and ongoing conditions at Screening will be presented by treatment group and overall, for the Safety Population. A listing of all the medical conditions for all subjects in the Safety Population will also be provided.

6.8 Prior and Concomitant Medications

Separate tabulations will be produced for prior and concomitant medications presented by treatment group and overall, for the Safety Population. For reporting purposes, prior medications are defined as all medications taken within 30 days of the Screening visit but stopping before the date of first dose of study drug. Concomitant medications are defined as medications taken on or after the date of first dose of study drug, including medications initiated prior to the first dose of study drug and continuing after first dose of study drug. Medications for which a stop date is not recorded will be designated ongoing at end of study. Prior and concomitant medications will be summarized using Anatomic Therapeutic Chemical (ATC) Level 3 and Preferred Name.

[redacted]

[redacted]

6.9 Exposure to Study Drug

Extent of exposure (number of days of exposure to study drug) will be presented by treatment group for the Safety Population.

6.10 Treatment Compliance

Treatment compliance, calculated as defined in Section 6.2.9, will be presented by treatment group per visit interval (Visit 2 to Visit 4, Visit 4 to Visit 5, and Visit 5 to Visit 6) for the Safety Population.

6.11 Efficacy Analyses

All statistical tests will be performed using a two-tailed 5% overall significance level, unless otherwise stated. All comparisons between treatments will be reported with 95% confidence intervals (CI) for the difference, unless otherwise stated.

6.11.1 Primary Endpoint

The primary efficacy endpoint is the change from baseline to Week 12 in the weekly mean of the NRS score assessing average pain intensity related to DPN in the past 24 hours.

The hypothesis that will be tested is as follows:

$$H_0 = \mu_{NYX,50\,mg} - \mu_{placebo} = 0 \qquad \text{versus} \qquad H_1 = \mu_{NYX,50\,mg} - \mu_{placebo} \neq 0$$

Where $\mu_{NYX,50\,mg}$ denotes the mean change from baseline to Week 12 in the weekly mean of the NRS score in the NYX-2925 50 mg treatment group,

And $\mu_{placebo}$ denotes the mean change from baseline to Week 12 in the weekly mean of the NRS score in the placebo group.

[redacted]

[redacted]

6.11.1.1 Estimand

The treatment-policy estimand will allow estimation of the improvement (reduction) from Baseline in the weekly mean of the daily NRS score in all subjects, irrespective of early discontinuation from treatment.

The following four attributes describe the estimand that will be used to define the treatment effect of interest for the primary efficacy analysis:

1. Population = Subjects meeting the protocol-specified inclusion/exclusion criteria, who received at least one dose of study drug and who have at least one post-baseline assessment of the pain intensity NRS.
2. Subject-level outcome = Change from baseline in the weekly mean of the daily NRS score assessing average pain intensity in the past 24 hours
3. Intercurrent event handling = An intercurrent event is defined as discontinuation of study drug due to an AE or lack of efficacy prior to Week 12 (where Action Taken with Study Drug (following AE) = "Study Drug Withdrawn" or Primary Reason for Withdrawal = "Adverse Event" or "Lack of Efficacy"). Missing data will not be imputed, and the missing values will be assumed to follow the missing-at-random (MAR) mechanism.
4. Population-level summary measure = Difference in least squares (LS) mean change from baseline in the weekly mean of the daily NRS score at Week 12, comparing NYX-2925 50 mg QD to placebo.

6.11.1.2 Primary Efficacy Analysis

A restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) will be utilized to analyze the change from baseline to Week 12 in the weekly mean of the NRS score assessing average pain intensity related to DPN in the past 24 hours.

The MMRM model will have site, treatment group, week, baseline NRS score, and treatment-by-week interaction as terms in the model. The unstructured covariance (UN) will be utilized as the within-subject covariance structure. in the event that the model fails to converge using the UN, the covariance structure among Toeplitz (TOEP), first-order autoregressive [AR(1)], and compound symmetry (CS) for which the model converges and yields the least corrected Akaike's information criterion (AICC) will be used. The Kenward-Roger degrees of freedom correction will also be used for this analysis.

[redacted]

[redacted]

The estimate of the treatment difference at Week 12 and standard error (SE) will be derived from this model. Observed NRS scores at baseline and at each week, as well as their change from baseline at each week will be presented by treatment group. The LS means, corresponding SEs, and 95% CI for each treatment group, as well as the estimate, corresponding SE, and p-value of the treatment difference in LS means at each week will be presented.

The following is the sample SAS code that will be used for this analysis:

```
PROC MIXED DATA= DATAIN;
CLASS USUBJID TREATMENT WEEK SITE;
MODEL CFB = TREATMENT WEEK SITE TREATMENT*WEEK BASELINE / DDFM=KR;
REPEATED WEEK / SUBJECT=USUBJID TYPE=UN;
LSMEANS TREATMENT*WEEK / CL DIFF;
RUN;
```

A line plot showing the LS means and 95% CIs of the weekly mean NRS scores from Week 1 through Week 12 for each treatment group will be presented.

6.11.1.3 Sensitivity Analyses

6.11.1.3.1 Pattern-Mixture Model

To assess the robustness of the results to deviations from the MAR assumption in the primary analysis, a sensitivity analysis will be conducted such that non-monotone missing data is imputed under the MAR assumption while the monotone data is imputed under the missing not at random (MNAR) assumption (i.e., that missingness is also dependent on the unobserved variable values).

This analysis will therefore provide a stress test of the MAR assumption in the primary analysis and will provide a conservative estimate of the treatment effect.

The pattern-mixture modeling will be implemented by first turning the non-monotone missing data pattern into a monotone missing pattern under the MAR assumption using the Markov Chain Monte Carlo (MCMC) method in SAS' PROC MI with the IMPUTE = MONOTONE and the PRIOR = JEFFREYS options to specify a non-informative prior for the imputation process. Then the MONOTONE statement along with the MNAR statement with option MODEL in SAS' PROC MI will be utilized to implement the MNAR assumptions and control-based pattern imputation[2,3]. The inference of this sensitivity analysis will be based on the combined estimates using the standard multiple imputation technique via Rubin's[4] rules.

[redacted]

[redacted]

Missing data will be imputed using a pattern-mixture model approach that uses a control-based pattern imputation. With this approach, subjects who discontinued from the NYX-2925 treatment group will be assumed to follow a similar outcome trajectory as subjects from the placebo (control) group, and subjects who discontinued from placebo (control) group are modeled as completers within their own group (MAR within control group). That is, the imputation model for the missing observations in the NYX-2925 treatment group is constructed not from the observed data in the NYX-2925 treatment group, but rather from the observed data in the placebo group. This model is also the imputation model that will be used to impute missing observations in the placebo group. The missing values for each variable will be imputed based on a model simulated from the posterior predictive distribution of the conditional regression model fitted on the imputed variable using only the observations from the placebo group. This will be implemented by utilizing the MONOTONE REG statement and MNAR statement with option MODEL of SAS' PROC MI with options nimpute=20 and seed=373613962.

The following is the sample SAS code that will be used to implement the control-based pattern mixture imputation:

```
PROC MI DATA=DATAIN OUT=DATAIN_MONO SEED=373613962 NIMPUTE=1;
BY TREATMENT;
VAR BASELINE NRS_Week1-NRS_Week12;
MCMC CHAIN=MULTIPLE IMPUTE=MONOTONE PRIOR = JEFFREYS;
RUN;

PROC MI DATA= DATAIN_MONO SEED=373613962 NIMPUTE=20
OUT=DATA_IMPUTED;
CLASS TREATMENT SITE;
MONOTONE REG(NRS_Week1-NRS_Week12);
MNAR MODEL(NRS1_Week1-NRS_Week12 /
MODELOBS=(TREATMENT='Placebo'));
VAR SITE BASELINE NRS_Week1-NRS_Week12;
RUN;
```

Once all the weekly mean NRS scores are imputed, the change from baseline at each week will be calculated and consequently will be analyzed using the same MMRM model employed in the primary analysis.

The following sample SAS code will be used:

[redacted]

[redacted]

```
PROC MIXED DATA= IMPUTED_ALL;
BY _IMPUTATION_;  /* 20 sets of results produced */
CLASS USUBJID TREATMENT WEEK SITE;
MODEL CFB = TREATMENT WEEK SITE TREATMENT*WEEK BASELINE /
DDFM=KR;
REPEATED WEEK / SUBJECT=USUBJID TYPE=UN;
LSMEANS TREATMENT TREATMENT*WEEK / CL DIFF;
ODS OUTPUT LSMEANS=LSMEANS DIFFS=DIFFS;
RUN;
```

Then the results are to be summarized using PROC MIANALYZE, where the treatment group LS means and their differences between treatments will be combined across all 20 imputed datasets:

```
PROC SORT DATA= LSMEANS; BY TREATMENT WEEK _IMPUTATION_; RUN;

PROC MIANALYZE PARMS= LSMEANS;
MODELEFFECTS ESTIMATE;
STDERR STDERR;
ODS OUTPUT PARAMETERESTIMATES= LSMEANS_COMB;
BY TREATMENT WEEK;
RUN;

PROC SORT DATA= DIFFS; BY TREATMENT;
RUN;

PROC MIANALYZE PARMS= DIFFS(WHERE=(WEEK=_WEEK));
MODELEFFECTS ESTIMATE;
STDERR STDERR;
ODS OUTPUT PARAMETERESTIMATES= DIFFS_COMB;
BY TREATMENT;
RUN;
```

LS means, SEs, and 95% CIs for each treatment group based on the imputed data will be presented at each week as well as the estimate of treatment difference, SE, and p-value at each week with Week 12 as the primary timepoint of interest.

6.11.1.3.2 Tipping Point Analysis

If the primary efficacy analysis in Section 6.11.1.2 significantly favors NYX-2925, a tipping point sensitivity analysis[4] for the primary efficacy endpoint will be conducted to investigate how severe

[redacted]

[redacted]

the departure from the MAR assumption data must be to overturn conclusion from the primary analysis.

In this analysis, the assumption will be that that missing data in the NYX-2925 group follows a MNAR pattern. A tipping point-based approach will be used such that the trajectories of the subjects in the NYX-2925 group after early withdrawal are assumed to be worse than placebo by a fixed amount (δ). The value of δ is the adjustment added during imputation to the change from baseline NRS scores at each visit after study discontinuation. This increment is added only to the imputed change from baseline NRS scores at visits after study discontinuation of the subjects in NYX-2925. The value of δ will increase in increments of 0.1 (i.e., 0.1, 0.2, 0.3) up to the point at which the treatment difference at Week 12 is no longer statistically significant. This analysis provides a measure of the degree by which the subjects in the NYX-2925 group who discontinued early would need to be worse at each post-discontinuation visit in order for the null hypothesis of no treatment difference to no longer be rejected. Each imputed dataset produced through PROC MI procedure will be processed as follows:

- All values imputed for the placebo group will remain unchanged
- All values imputed for the NYX-2925 group will be incremented by a value of δ, which will vary from 0 up to a value by which statistical significance is not reached
- The modified data will be analyzed using similar analysis as described in Section 6.11.1.

Results will then be combined using PROC MIANALYZE and will consequently be recorded.

The "tipping point" is defined as the value of δ at which the result changes from statistically significant treatment effect to a treatment effect that is no longer statistically significant. The larger the value of δ, the more robust the conclusion from the primary analysis, with respect to assumptions around missing data.

6.11.1.4 Supportive Analysis

6.11.1.4.1 Analysis of Covariance on change from baseline to Week 12 in the weekly mean of the NRS score assessing average pain intensity related to DPN in the past 24 hours

To assess the robustness of the result observed for the primary endpoint, an Analysis of Covariance (ANCOVA) model with site and treatment as factors, and baseline NRS score as a covariate will be employed as a supportive analysis.

The following is the sample SAS code that will be used to implement this analysis:

[redacted]

[redacted]

```
PROC MIXED DATA= DATAIN;
CLASS TREATMENT SITE;
MODEL CFB_WEEK12 = TREATMENT SITE BASELINE / SOLUTION;
LSMEANS TREATMENT / CL DIFF;
RUN;
```

The LS means, SEs, and 95% CIs will be provided for each treatment group, as well as treatment difference estimate, SE, and p-value at Week 12.

[redacted]

[redacted]

[redacted]

[redacted]

6.11.2 Secondary Endpoints

All secondary endpoints will be analyzed using the mITT population. The secondary endpoints of this study are as follows:

6.11.2.1 Change from baseline in the weekly mean of the Daily Sleep Interference Scale (DSIS) scores at Week 12

A similar approach in modeling the REML-based MMRM as in the primary analysis will be applied to the change from baseline in the weekly mean of the DSIS scores at Week 12 except that the outcome variable will be change from baseline in the weekly mean of the DSIS scores at Weeks 1 through 12, and the fixed effects are as follows: site, treatment group, week, baseline DSIS score, and treatment-by-week interaction as terms in the model. Observed NRS scores at baseline and at each week, as well as the change from baseline NRS scores at each week will be presented by treatment group. The LS means, corresponding SEs, and 95% CIs for each treatment group will also be presented at each week. Additionally, the estimate, corresponding SE, and p-value of the treatment difference at Week 12 will also be presented.

[redacted]

[redacted]

[redacted]

Subgroup analyses as described in Section 6.11.1.5 may also be performed for this endpoint.

6.11.2.2 Percentage of subjects 'much improved' or 'very much improved' on the Patient Global Impression of Change by Visit

The number and percentage of subjects reporting each of the response levels will be summarized by treatment for Weeks 4, 8, and 12.

Analysis will utilize the Cochran-Mantel-Haenszel (CMH) test to compare the treatment groups, using the following SAS code:

```
PROC FREQ DATA=CMHDATA1;
TABLES TREATMENT*RESP / RISKDIFF CMH;
ODS OUTPUT RISKDIFFCOL2 = RISK CMH = CMH_PVAL;
RUN;
```

The number and percentage of subjects 'much improved' or 'very much improved' by treatment at each visit will be presented. The risk difference for NYX-2925 vs placebo, corresponding 95% CI and p-value for the CMH statistic also be provided by visit.

Summary statistics for the PGI-C as a continuous score will also be provided by treatment group at each visit. Scores will be analyzed using the same REML-based MMRM as in the primary analysis, except with the exclusion of a baseline covariate.

Observed scores at each week (4, 8, and 12) will be presented by treatment group. The LS means, corresponding SEs, and 95% CIs for each treatment group will be presented at each week along with the LS mean difference, corresponding SE, and p-value.

A listing of all PGI-C scores will also be provided.

6.11.2.3 Percentage of subjects achieving ≥30% and ≥50% reduction from baseline in the weekly mean NRS average pain intensity related to DPN at Week 12

Percentage of subjects achieving both ≥30% and ≥50% reduction from baseline in the weekly mean NRS average pain intensity related to DPN at Week 12 will be analyzed and presented as described in Section 6.11.2.2.

[redacted]

[redacted]

6.11.2.4 Change from baseline to Week 12 in Norfolk Quality of Life Questionnaire – Diabetic Neuropathy score

A similar approach in modeling the REML-based MMRM as in the primary analysis will be applied to the change from baseline to Week 12 in the QOL-DN total score except that the outcome variable will be change from baseline to Weeks 4 and 12 in the QOL-DN total score, and the fixed effects are as follows: site, treatment group, week, baseline QOL-DN total score, and treatment-by-week interaction as terms in the model.

Observed QOL-DN total scores at baseline and at each week (4 and 12), as well as the change from baseline QOL-DN total scores at each week (4 and 12) will be presented by treatment group. The LS means, corresponding SEs, and 95% CIs for each treatment group will also be presented at each week (4 and 12). Additionally, estimate, corresponding SE, and p-value of the treatment difference at Week 12 will also be presented.

Listing of the QOL-DN individual item scores, as well as the domain scores at baseline and at Weeks 4 and 12 will be presented.

6.11.2.5 Use of rescue medication, including the proportion of subjects using rescue medication, the frequency and amount used

The total number of tablets taken and percentage of rescue-free days per week will be summarized by treatment group.

The proportion of subjects that used rescue medication (one or more tablets) at any point after the first dose of study drug will also be summarized by treatment group. A Z-test on equality of two proportions will be performed to compare the treatment groups, using the following SAS code:

```
PROC FREQ DATA=DATIN ORDER=DATA;
   TABLES TREATMENT*RESPONDER / RISKDIFF(EQUAL VAR=NULL CL=WALD);
   ODS OUTPUT PDIFFCLS = DIFF PDIFFTEST = PVAL;
RUN;
```

A similar approach in modeling the REML-based MMRM as in the primary analysis will be applied to the weekly dosage of acetaminophen used except that the outcome variable will be the dosage of acetaminophen used at Weeks 1 through 12, and the fixed effects are as follows: study site, treatment group, week, and treatment-by-week interaction as terms in the model. The LS means, corresponding SEs, and 95% CIs for each treatment group will also be presented at each

[redacted]

[redacted]

week. Additionally, estimate, corresponding SE, and p-value of the treatment difference at each week will also be presented.

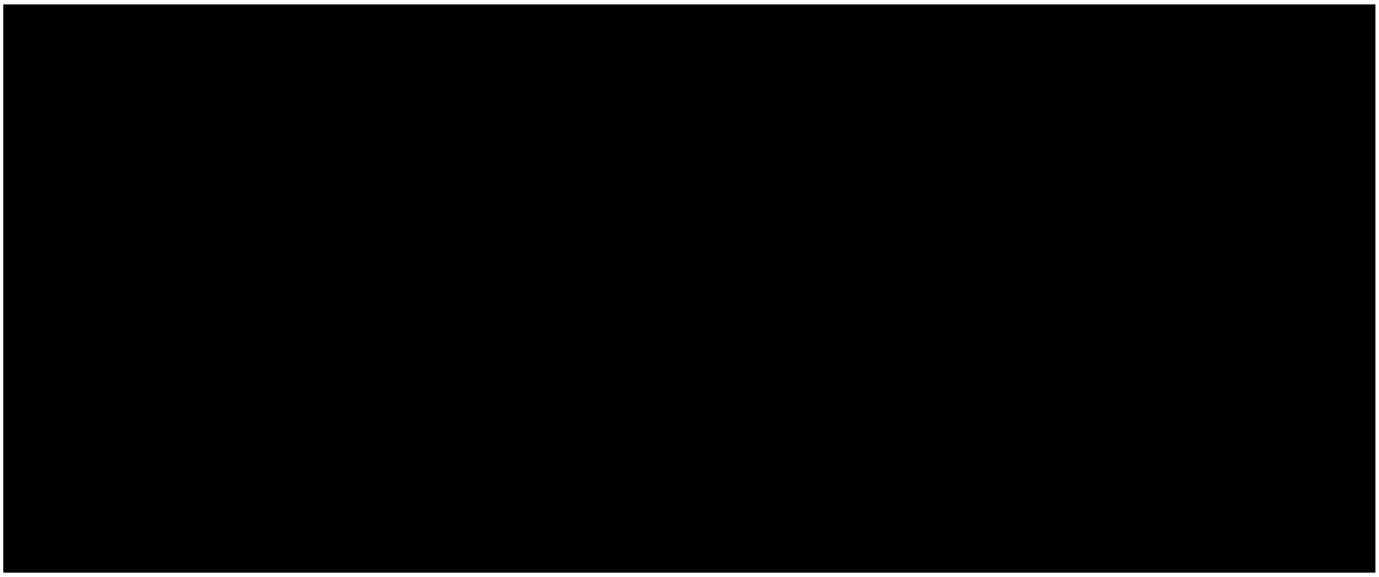
6.11.2.6 Cumulative response (percent reduction from baseline) in the weekly mean NRS average pain intensity at Week 12

A cumulative responder analysis will be conducted for the primary efficacy endpoint. in this analysis, response is defined as any percent reduction from baseline in the weekly mean NRS average pain intensity at Week 12. Subjects who do not achieve a reduction from baseline at Week 12, who have a missing result, or who prematurely discontinue from treatment prior to Week 12 will be defined as a non-responder (i.e., 0% reduction/improvement in percent reduction from baseline). A cumulative response curve will be generated in which the response level is on the x-axis (0-100%, in 10% intervals, with reference lines at 30% and 50%) while the associated cumulative proportion of subjects calculated for that response level (i.e., percent reduction from baseline) is on the y-axis. The difference in the cumulative response curves between treatment groups will be analyzed using a Kolmogorov-Smirnov test. This test determines if two samples of data are from the same distribution. The D statistic and associated p-value will be provided.

```
PROC NPAR1WAY DATA= DATAIN;
CLASS TREATMENT;
VAR RESP;
EXACT KS;
RUN;
```

6.11.3 Other Efficacy Endpoints

[redacted]



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6.11.4 Multiplicity

No multiplicity adjustment will be made on the secondary and other efficacy endpoints.

6.12 Safety Analyses

Safety analyses will be summarized by treatment received for the Safety Analysis Set.

[redacted]

[redacted]

6.12.1 Adverse Events

Adverse events will be collected from the time of study drug administration through the last day of the subject's participation in the study.

A treatment emergent adverse event (TEAE) is defined as:

- Any AE that has an onset on or after the first dose of study drug, through the last day of the subject's participation in the study
- Any pre-existing AE that has worsened in severity on or after the first dose of study drug, through the last day of the subject's participation in the study

A treatment-related AE is defined as an AE classified by the Investigator as 'Related' to the study drug. If an AE has missing relationship it is assumed to be related to the study drug for analysis purposes.

Maximum severity (Life threatening) will be assumed for an AE with missing severity.

An overall summary table of AE incidence (number and percent of subjects) and number of events, will be presented by treatment group and overall, for the following categories:

- Any TEAE
- Treatment-Related TEAEs
- Serious TEAEs
- Serious Treatment-Related TEAEs
- TEAEs Leading to Study Drug Discontinuation
- TEAEs Leading to Early Withdrawal
- TEAEs Leading to Death

Summaries of TEAE incidence and number of events by SOC and PT will be presented by treatment group and overall, for the following:

- TEAEs
- Treatment-related TEAEs
- Serious TEAEs
- Serious Treatment-Related TEAEs
- TEAEs Leading to Study Drug Discontinuation
- TEAEs by Maximum Severity, (incidence only)

[redacted]

[redacted]

- Treatment-Related TEAEs by Maximum Severity, (incidence only)

The following listings of AEs will be presented in Section 14.3.2 of the CSR:

- Serious AEs
- AEs Leading to Early Withdrawal
- AEs Leading to Death

AE tabulations will be presented by SOC and PT in descending overall frequency of AE incidence and then alphabetically for ties.

All reported AEs will be listed in Appendix 16.2.7 of the CSR.

6.12.2 Laboratory Data

Descriptive statistics for the observed values and change from baseline will be presented by treatment group and visit for each hematology, urinalysis, and serum chemistry (including triglycerides and thyroid panel) parameter. Each continuous measurement will be classified as below, within, or above normal range, based on ranges supplied by the laboratory used. Categorical parameters may also be classified as normal or abnormal based on normal ranges, and subject counts within each category will be summarized. Shift tables in relation to the normal range from baseline to each post-baseline visit will be presented.

Summaries and listings will be presented using the original unit for each parameter as received from the analytical laboratory.

A listing of out of normal range laboratory values throughout the study will be presented. All laboratory assessments, including urine pregnancy tests, drug tests, and serology will also be listed.

A separate listing will be provided for all Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), and Bilirubin results at all timepoints for any subjects who meet the criteria for liver function abnormalities as defined in Section 6.2.25.

6.12.3 Vital Signs

Descriptive statistics for observed values and changes from baseline in the following vital signs will be tabulated at each post-baseline visit:

- Systolic blood pressure (mmHg)

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- Diastolic blood pressure (mmHg)
- Pulse rate (bpm)
- Body weight (kg)

All vital signs measurements throughout the study will be listed.

6.12.4 Physical Examination

All physical examination collection data (including brief physical examination) will be listed.

6.12.5 Electrocardiogram Data

Descriptive statistics for observed values and changes from baseline in the following ECG variables will be tabulated at each post-baseline visit:

- Heart rate (bpm)
- PR interval (ms)
- RR interval (ms)
- QRS complex (ms)
- QT interval (ms)
- QTc interval (ms) [Bazett's formula - QTcB]
- QTc interval (ms) [Fridericia's formula - QTcF]

Shift tables in relation to the overall interpretation (Normal, Abnormal Not Clinically Significant [NCS], and Abnormal Clinically Significant [CS]) from baseline to each post-baseline visit will be presented.

All ECG assessments throughout the study will be listed.

6.12.6 Sheehan-Suicidality Tracking Scale

Descriptive statistics for observed and change from baseline S-STS total score will be summarized by treatment group for each post-baseline visit.

All S-STS responses throughout the study will be listed.

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6.12.7 Misuse, Abuse, and Diversion Drug Event Reporting System

Potentially aberrant drug behavior (i.e., misuse and abuse-related events) will be identified, assessed, and quantified using the Misuse, Abuse, and Diversion Drug Event Reporting System (MADDERS®), which consists of a set of forms completed by Investigators or qualified Sub-investigators when potential abuse-related events are identified and upon the completion of each subject's participation in the study. Any misuse and abuse-related event will be recorded as an adverse event. A separate independent report will be provided by the data vendor for inclusion in the CSR.

7 INTERIM ANALYSIS

No interim analyses are planned.

8 DATA SAFETY MONITORING BOARD ANALYSIS

No data safety monitoring board (DSMB) analyses are planned.

9 CHANGES TO PLANNED PROTOCOL ANALYSIS

1. The primary endpoint was clarified from "*change from baseline in the weekly mean NRS score assessing average pain intensity related to DPN in the past 24 hours*" to "*change from baseline **to Week 12** in the weekly mean NRS score assessing average pain intensity related to DPN in the past 24 hours.*".
2. For the primary efficacy analysis, intercurrent event handling, missing data will not be imputed (using baseline observation carried forward [BOCF], as described in the protocol), and the missing values will be assumed to follow the missing-at-random (MAR) mechanism.
3. The secondary efficacy endpoint "*Change from baseline in the weekly mean of the daily Numerical Rating Scale (NRS) at each week from Week 1 through Week 12*" was updated to "*Change from baseline in the weekly mean Numerical Rating Scale (NRS) score assessing average pain intensity related to DPN at each week from Week 1 through Week 12*".

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4. One of the other efficacy endpoints was updated as follows "Change from baseline in the weekly mean NRS score assessing ~~average~~ pain intensity upon walking in the past 24 hours ~~from baseline~~"
5. The other efficacy endpoint "*Change from baseline in the mean NRS score for daily worst pain intensity related to DPN*" was updated to "*Change from baseline in the weekly mean NRS score assessing worst pain intensity related to DPN*"
6. Other efficacy endpoint "*Change from baseline to Week 12 in Norfolk Quality of Life Questionnaire – Diabetic Neuropathy (QOL-DN) domain scores*" was added.
7. The time to first ≥30% (and ≥50%) reduction will be identified based on a moving average of the NRS average pain intensity, that is, NRS average from Day 1 to Day 7, from Day 2 to Day 8, from Day 3 to Day 9, up to from Day 78 to Day 84. The first moving average that yields a reduction from baseline of ≥30% (and ≥50%) will be identified and the last day of this block of 7 days on which the reduction was identified will be the time to first of ≥30% (and ≥50%) reduction which is different to how the weekly NRS is define for the primary endpoint, and any other efficacy endpoints based on the daily NRS scores.
8. Censoring of the subjects who failed to achieve the target reduction (≥30% and ≥50%) was changed from "*the time of their final week with NRS pain intensity measurements*" to "*the day that the last available NRS pain intensity score was recorded*"
9. Sustainability of ≥30% reduction and ≥50% reduction of weekly mean NRS average pain intensity related to DPN will not be formally analyzed.
10. Multiplicity adjustment was changed from "*The primary efficacy endpoint and other selected efficacy endpoints will be tested (using MMRM as described above) in a hierarchical manner to preserve the overall Type I error rate. There will be no adjustment for multiple comparisons for other efficacy endpoints*" to "*No multiplicity adjustment will be made on the secondary and other efficacy endpoints*".

[redacted]

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10 REFERENCES

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2. Yuan, Y. (2014). Sensitivity Analysis in Multiple Imputation for Missing Data. *SAS Global Forum 2014 Conference*. Retrieved from: http://support.sas.com/resources/papers/proceedings14/SAS270-2014.pdf
3. Li, L. (2019). SAS® V9. 4 MNAR statement for multiple imputations for missing not at random in longitudinal clinical trials. *PharmaSUG 2019 Conference*. Retrieved from https://www.pharmasug.org/proceedings/2019/ST/PharmaSUG-2019-ST-103.pdf
4. Ratitch B, O'Kelly M, Tosiello R. Missing Data in Clinical Trials: from Clinical Assumptions to Statistical Analysis using Pattern Mixture Models. *Pharmaceutical Statistics*, 2013, 12(6), 337-347.
5. Rubin, D. B. (1976), "Inference and Missing Data,"Biometrika, 63, 581–592.

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11 LIST OF TABLES, FIGURES AND LISTINGS

The following table includes details of the tables, figures, and listings to be included within each section of the electronic common technical document (eCTD). The eCTD section is shown in bold. The following validation methods maybe used:

- Independent programming of values and manual review of format (IP)
- Independent programming by statistician of values and manual review of format (Stat IP)
- Manual review (MR)

Table Number	Table Title	Validation Method	Shell Number (If Repeat)
14.1	**Demographics Data**		
14.1.1	**Disposition**		
14.1.1.1	Subject Disposition, Early Withdrawals - Screened Population	IP	
14.1.1.2	Subject Disposition, Screen Failures - Screened Population	IP	
14.1.1.3	Populations by Site - Randomized Population	IP	
14.1.1.4	Protocol Deviations - Safety Population	IP	
14.1.2	**Demographics**		
14.1.2.1	Demographics and Baseline Characteristics - Safety Population	IP	
14.1.3	**Baseline Characteristics**		
14.1.3.1	Medical History Prior To Baseline by System Organ Class and Preferred Term - Safety Population	IP	
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14.1.4.1	Medications Prior to Baseline by ATC Level 3 and Preferred Name - Safety Population	IP	
14.1.4.2	Medications Ongoing at Baseline by ATC Level 3 and Preferred Name - Safety Population	IP	14.1.4.1
14.1.5.1	Patient Global Impression of Severity at Baseline - Safety Population	IP	
14.1.6.1	Neurological Examination at Baseline - Safety Population	IP	
14.2	**Efficacy Data**		
14.2.1	**Primary Efficacy Endpoint**		
14.2.1.1.1	Primary Endpoint: Average Pain Intensity Related to DPN, Change from Baseline in Weekly Mean NRS Score, Mixed Model for Repeated Measures - Modified Intent-to-Treat Population	Stat IP	

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14.2.1.1.2	Sensitivity Analysis (1): Average Pain Intensity Related to DPN, Change from Baseline to Week 12 in Weekly Mean NRS Score, Mixed Model for Repeated Measures, Imputation Using Pattern-Mixture Model - Modified Intent-to-Treat Population	Stat IP	14.2.1.1.1
14.2.1.1.3	Sensitivity Analysis (2): Average Pain Intensity Related to DPN, Change from Baseline in Weekly Mean NRS score at Week 12, Tipping Point Analysis - Modified Intent-to-Treat Population	Stat IP	
14.2.1.1.4	Supportive Analysis: Average Pain Intensity Related to DPN, Change from Baseline in Weekly Mean NRS Score at Week 12, Analysis of Covariance - Modified Intent-to-Treat Population	Stat IP	
14.2.1.2.1	Exploratory Analysis (1): Average Pain Intensity Related to DPN, Change from Baseline to Week 12 in Weekly Mean NRS Score, By Baseline NRS Score, Mixed Model for Repeated Measures - Modified Intent-to-Treat Population	Stat IP	14.2.1.1.1
14.2.1.2.2	Exploratory Analysis (2): Average Pain Intensity Related to DPN, Change from Baseline to Week 12 in Weekly Mean NRS Score, Adjusted by Baseline BPI-DN Interference Composite Score, Mixed Model for Repeated Measures - Modified Intent-to-Treat Population	IP	14.2.1.1.1
14.2.1.2.3	Exploratory Analysis (3): Average Pain Intensity Related to DPN, Change from Baseline to Week 12 in Weekly Mean NRS Score, Adjusted by Baseline DSIS Score, Mixed Model for Repeated Measures - Modified Intent-to-Treat Population	IP	14.2.1.1.1
14.2.1.2.4	Exploratory Analysis (4): Average Pain Intensity Related to DPN, Change from Baseline to Week 12 in Weekly Mean NRS Score, Adjusted by Duration of DPN at Baseline, Mixed Model for Repeated Measures - Modified Intent-to-Treat Population	IP	14.2.1.1.1
14.2.1.2.5	Exploratory Analysis (5): Average Pain Intensity Related to DPN, Change from Baseline to Week 12 in Weekly Mean NRS Score, Adjusted by Duration of Painful DPN at Baseline, Mixed Model for Repeated Measures - Modified Intent-to-Treat Population	IP	14.2.1.1.1
14.2.1.3.1	Subgroup Analysis (1): Average Pain Intensity Related to DPN, Change from Baseline to Week 12 in Weekly Mean NRS Score, By Baseline NRS score, Mixed Model for Repeated Measures - Modified Intent-to-Treat Population	IP	14.2.1.1.1
14.2.1.3.2	Subgroup Analysis (2): Average Pain Intensity Related to DPN, Change from Baseline to Week 12 in Weekly Mean NRS Score, By Prior Analgesic Use, Mixed Model for Repeated Measures - Modified Intent-to-Treat Population	IP	14.2.1.1.1

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14.2.1.3.3	Subgroup Analysis (3): Average Pain Intensity Related to DPN, Change from Baseline to Week 12 in Weekly Mean NRS Score, By Subjects Sourced Via AES, Mixed Model for Repeated Measures - Modified Intent-to-Treat Population	IP	14.2.1.1.1
14.2.1.3.4	Subgroup Analysis (4): Average Pain Intensity Related to DPN, Change from Baseline to Week 12 in Weekly Mean NRS Score, By Subjects Sourced Via AES and Baseline NRS Score, Mixed Model for Repeated Measures - Modified Intent-to-Treat Population	IP	14.2.1.1.1
14.2.2	**Secondary Efficacy Endpoints**	IP	
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14.2.2.2.1	Patient Global Impression of Change, Percentage of Subjects 'Much Improved' or 'Very Much Improved' by Visit - Modified Intent-to-Treat Population	IP	
14.2.2.2.2	Patient Global Impression of Change, Change from Baseline by Visit - Modified Intent-to-Treat Population	IP	
14.2.2.3	Average Pain Intensity Related to DPN, Percentage of Subjects Achieving ≥30% Reduction or ≥50% Reduction in Weekly Mean NRS Score at Week 12 - Modified Intent-to-Treat Population	IP	
14.2.2.4	Norfolk Quality of Life-Diabetic Neuropathy Scores, Change from Baseline to Week 12, Mixed model for Repeated Measures - Modified Intent-to-Treat Population	IP	
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14.2.2.6	Rescue Medication (Acetaminophen 500 mg), Percentage of Rescue-Free Days Per Week, Descriptive Statistics - Modified Intent-to-Treat Population	IP	
14.2.2.7	Proportion of Subjects Using Rescue Medication (Acetaminophen 500 mg) During the Study, Z-Test for Equality of Proportions - Modified Intent-to-Treat Population	IP	
14.2.2.8	Rescue Medication (Acetaminophen), Weekly Mean Dose Up to Week 12, Mixed Model for Repeated Measures - Modified Intent-to-Treat Population	IP	14.2.1.1.1
14.2.2.9	Average Pain Intensity Related to DPN, Cumulative Response (Percent Reduction from Baseline) in the Weekly Mean NRS Score at Week 12 - Modified Intent-to-Treat Population	IP	

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14.2.3	**Other Efficacy Endpoints**		
14.2.3.1.1	Average Pain Intensity Upon Walking, Change from Baseline to Week 12 in Weekly Mean NRS Score, Mixed Model for Repeated Measures - Modified Intent-to-Treat Population	IP	14.2.1.1.1
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14.2.3.2.1	Worst Pain Intensity Related to DPN, Change from Baseline to Week 12 in Weekly Mean NRS Score, Mixed Model for Repeated Measures - Modified Intent-to-Treat Population	IP	14.2.1.1.1
14.2.3.2.2	Subgroup Analysis: Worst Pain Intensity Related to DPN, Change from Baseline to Week 12 in Weekly Mean NRS Score in Subjects with Mean Score ≥4 at Baseline, Mixed Model for Repeated Measures - Modified Intent-to-Treat Population	IP	14.2.1.1.1
14.2.3.3	Brief Pain Inventory for Diabetic Peripheral Neuropathy, Change from Baseline to Week 12, Mixed Model for Repeated Measures - Modified Intent-to-Treat Population	IP	
14.2.3.4	Average Pain Intensity Related to DPN, Time to First ≥30% Reduction (Days) in Mean NRS Score - Modified Intent-to-Treat Population	IP	
14.2.3.5	Average Pain Intensity Related to DPN, Time to First ≥50% Reduction (Days) in Mean NRS Score - Modified Intent-to-Treat Population	IP	
14.2.3.6	Pain Catastrophizing Scale, Change from Baseline to Week 12, Analysis of Covariance - Modified Intent-to-Treat Population	IP	
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14.3.1.4	Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term - Safety Population	IP	14.3.1.2
14.3.1.5	Serious Treatment Emergent Adverse Events Related to Study Drug by System Organ Class and Preferred Term - Safety Population	IP	14.3.1.2

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14.3.1.6	Treatment Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term - Safety Population	IP	14.3.1.2
14.3.1.7	Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity - Safety Population	IP	
14.3.1.8	Treatment Emergent Adverse Events Related to Study Drug by System Organ Class, Preferred Term and Maximum Severity - Safety Population	IP	14.3.1.7
14.3.2	**Listings of Deaths, Other Serious and Significant Adverse Events**	IP	
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14.3.7.2	Hematology Data, Normal Range Shifts - Safety Population	IP	
14.3.7.3	Serum Chemistry Data, Descriptive Statistics - Safety Population	IP	14.3.7.1
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14.3.7.7	Urinalysis Data, Descriptive Statistics - Safety Population	IP	
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14.3.7.9	Sheehan-Suicidality Tracking Scale, Change from Baseline - Safety Population	IP	

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14.3.8.1	Concomitants Medications by ATC Level 3 and Preferred Name - Safety Population	IP	

Figure Number	Figure Title	Validation Method	Shell Number (If Repeat)
14.2.1.1	Average Pain Intensity Related to DPN, Change from Baseline in Weekly Mean NRS Score, LS Mean (95% CI) - Line Plot - Modified Intent-to-Treat Population	MR	
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14.2.1.11	Average Pain Intensity Related to DPN, Weekly Mean NRS Score at Week 12 Versus Duration of DPN at Baseline - Scatter Plot - Modified Intent-to-Treat Population	MR	

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14.2.1.12	Average Pain Intensity Related to DPN, Weekly Mean NRS Score at Week 12 Versus Duration of Painful DPN at Baseline - Scatter Plot - Modified Intent-to-Treat Population	MR	

Listing Number	Listing Title	Validation Method	Shell Number (If Repeat)
16.2	**Subject Data Listings**		
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16.2.1.1	Subject Disposition, Early Withdrawal - Randomized Population	IP	
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16.2.4.1	Demographics and Baseline Characteristics - Safety Population	IP	
16.2.4.2	Medical History - Safety Population	IP	
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16.2.4.4	Confirmation of Diabetic Peripheral Neuropathy - Safety Population	IP	
16.2.4.5	Discontinuation of Analgesic Medications - Safety Population	IP	
16.2.5	**Compliance and / or Drug Concentration Data**	IP	
16.2.5.1	Study Drug Administration - Safety Population	IP	
16.2.5.2	Study Drug Dispensed and Returned - Safety Population	IP	
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16.2.6.2	Average Pain Intensity Upon Walking in the Past 24 Hours, Weekly Mean NRS Score - Modified Intent-to-Treat Population	IP	16.2.6.1

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16.2.6.3	Worst Pain Intensity Related to DPN in the Past 24 Hours, Weekly Mean NRS Score - Modified Intent-to-Treat Population	IP	16.2.6.1
16.2.6.4	Daily Rescue Medication (Acetaminophen 500 mg) Usage - Modified Intent-to-Treat Population	IP	
16.2.6.5	Daily Sleep Interference Scale - Modified Intent-to-Treat Population	IP	
16.2.6.6	Pain Catastrophizing Scale - Modified Intent-to-Treat Population	IP	
16.2.6.7	Brief Pain Inventory for Diabetic Peripheral Neuropathy - Modified Intent-to-Treat Population	IP	
16.2.6.8	Norfolk Quality of Life Questionnaire - Diabetic Neuropathy - Modified Intent-to-Treat Population	IP	
16.2.6.9	Patient Global Impression of Severity - Modified Intent-to-Treat Population	IP	
16.2.6.10	Patient Global Impression of Change - Modified Intent-to-Treat Population	IP	
16.2.6.11	Sheehan-Suicidality Tracking Scale - Modified Intent-to-Treat Population	IP	
16.2.6.12	Average Pain Intensity Related to DPN, Time to First ≥30% or ≥50% Reduction (Days) in Mean NRS Score - Modified Intent-to-Treat Population		
16.2.7	**Adverse Event Listings**	IP	
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16.2.7.1	Hematology Data - Safety Population	IP	
16.2.8.1	Serum Chemistry Data - Safety Population	IP	
16.2.8.2	Urinalysis Data - Safety Population	IP	
16.2.8.3	Thyroid Panel Data - Safety Population	IP	
16.2.8.4	Serology Data - Safety Population	IP	
16.2.8.5	Vital Signs Data - Safety Population	IP	
16.2.8.6	Electrocardiogram Data - Safety Population	IP	
16.2.8.7	Physical Examination Data - Safety Population	IP	
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16.2.8.9	Urine Pregnancy Testing Data - Safety Population	IP	
16.2.8.10	Urine Drug Screening Data - Safety Population	IP	

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