Statistical Analysis Plan

A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of NYX-2925 in Subjects with Fibromyalgia
Protocol Number: NYX-2925-2005,
Version 7.0 (Amendment 6)

Version 1.0
Issue Date: 21JUL2022

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A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of NYX-2925 in Subjects with Fibromyalgia

Protocol Number: NYX-2925-2005,
Version 7.0 (Amendment 6), dated 14Oct2021

Version 1.0

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Previous Versions

Not Applicable

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[redacted]

SAP Amendments Before Database Lock

Version	Issue Date	Section	Revision / Addition	Rationale
	Not Applicable			

[redacted]

[redacted]

1 INTRODUCTION

This document details the planned statistical analyses for the Aptinyx Inc, protocol NYX-2925-2005 study titled "A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of NYX-2925 in Subjects with Fibromyalgia".

The proposed analyses are based on Protocol Version 7.0 Amendment 6, dated [redacted].

This is a 13- to 16-week study that includes a 1- to 4-week Screening Period followed by a 12-week, double-blind, randomized, placebo-controlled Treatment Period in which subjects will take one capsule of study drug once daily by mouth for up to 12 weeks.

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 6 tablets total for pain associated with fibromyalgia, not to exceed 3 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 adverse event/serious adverse event (AE/SAE) closure and any newly reported SAEs.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are:

- To evaluate the efficacy of NYX-2925 taken orally once daily versus placebo for the treatment of fibromyalgia.
- To assess safety and tolerability of NYX-2925 taken orally once daily.

2.2 Secondary Objectives

The secondary objective of the study is:

- To assess effects of NYX-2925 taken orally once daily versus placebo on general pain, sleep interference, fatigue, physical functioning, psychological state and global improvement.

3 ENDPOINTS

3.1 Primary Endpoint

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

3.2 Secondary Endpoints

The secondary efficacy endpoints are:

- Percentage of subjects "much improved" or "very much improved" on the Patient Global Impression of Change (PGI-C) at Week 12.
- Change from baseline in the weekly mean of the Daily Sleep Interference Scale (DSIS) scores at Week 12.
- Percentage of subject achieving ≥30% pain reduction from baseline in the weekly mean NRS average pain intensity at Week 12.
- Percentage of subjects achieving ≥50% reduction from baseline in the weekly mean NRS average pain intensity related to fibromyalgia at Week 12.
- Change from baseline to Week 12 in the Fibromyalgia Impact Questionnaire - Revised (FIQR) score.
- Change from baseline to Week 12 in the Patient Reported Outcome Measurement Information System – Fibromyalgia ($PROMIS_{FM}$) sleep disturbance score.
- Change from baseline to Week 12 in the Patient Reported Outcomes Measurement Information System - (PROMIS) fatigue profile score.
- Change from baseline to Week 12 in the Patient Reported Outcomes Measurement Information System (PROMIS) physical function score.
- Cumulative response (percent reduction from baseline) in the weekly mean NRS average pain intensity at Week 12.
- Use of rescue medication, including the proportion of subjects using rescue medication, the frequency and amount used.
- Change from baseline in the weekly mean of the daily Numerical Rating Scale (NRS) at each week from Week 1 through Week 12.

[redacted]

3.3 Other Efficacy Endpoints

[redacted]

3.4 Safety Endpoints

The safety endpoints will include adverse events (AE), serious adverse events (SAE), discontinuation due to adverse events and the S-STS. Vital signs, physical examination, electrocardiogram and standard clinical laboratory parameters will also be assessed.

4 SAMPLE SIZE

The planned sample size is a total of 300 randomized subjects with 100 subjects per treatment group. Efficacy analyses will include all subjects who receive at least one dose of study drug and who have at least one post baseline assessment. It is expected that approximately 15% of subjects will be excluded from the efficacy population. A total of 85 subjects per treatment arm will provide approximately 88% power to detect a difference in means of 0.73 for NYX-2925 50 mg or 100 mg versus Placebo group assuming that the common standard deviation is 1.7 without correcting for multiple testing, using one-sided statistical testing with an overall Type I error rate of 0.05.

[redacted]

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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 7 days within the protocol-defined algorithm and whose compliance with daily diary completion is found to be 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 notified the site if the subject is "Eligible" or "Not eligible." No other information will be provided.

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 Population

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

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 are randomized.

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.

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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.

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 Race" 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).

[redacted]

6.2.5 Missing/Partial Start/Stop Date of Adverse Events 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 "01-Jan" of the same year or the date of the first dose of study drug whichever is latest. 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 or subject was not dosed, 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 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.

[redacted]

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- If the stop date occurs before the start of study drug subject was not dosed, 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 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.

6.2.8 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:

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

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:

[redacted]

[redacted]

- 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)

6.2.9 Inexact Values

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

6.2.10 Electrocardiogram (ECG) 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.

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

6.2.11 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.

[redacted]

[redacted]

Assessment(s)	Timing of Early Withdrawal Assessment	Mapped Visit
Physical Exam	Day 2+	Week 12
Vital signs, Laboratory samples, PGI-C, FIQR, PROMIS$_{FM}$, PROMIS, ECG	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

6.2.12 Unscheduled Visits

Unscheduled visits will be handled in an identical manner to early withdrawal assessments. 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.

6.2.13 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.

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

6.2.14 Percent Change from Baseline

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

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

6.2.15 Duration of Fibromyalgia

Duration of fibromyalgia at baseline (in years) will be calculated as date of first dose – onset date + 1 / 365.25. Onset date of fibromyalgia will be taken as reported on the medical history form.

[redacted]

[redacted]

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 52 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 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 average pain intensity related to fibromyalgia in the past 24 hours daily (from 4am to 4am of subsequent day) at bedtime in the handheld diary.

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

[redacted]

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)
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

[redacted]

Timing of Last Non-Missing Diary	Assigned Week (from which to count backwards)
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 6.2.13 and 6.2.14.

6.2.17.3. Definition of ≥30% and ≥50% Responder

Subjects who achieve a percent reduction in NRS score relating to 'Average pain intensity the past 24 hours' of ≥30% (programmatically, where the percent 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 in the past 24 hours' of ≥50% (programmatically, where the percent 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 fibromyalgia in the past 24 hours' at Week 12 will be classified as non-responders.

6.2.17.4 [redacted]

[redacted]

[redacted]

[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

[redacted]

[redacted]

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.

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 PGI-C response of 1 ('very much improved') or 2 ('much improved'), or non-responders, that is, all other PGI-C 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 Fibromyalgia Impact Questionnaire – Revised

Fibromyalgia Impact Questionnaire – Revised (FIQR) is questionnaire consisting of 21 individual questions in an 11-point numeric rating scale from 0 to 10 (where 10 correspond to 'worst'). The FIQR is divided into three domains: 'function' (containing 9 questions), 'overall impact' (containing 2 questions), 'symptoms' (containing 10 questions). The total FIQR score is calculated as the sum of three modified domain scores: the summed score for function divided by 3, the

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summed score for overall impact, the summed score for symptoms divided by 2. Higher FIQR scores indicate greater disease severity and impaired physical function.

6.2.22 Patient Reported Outcomes Measurement Information System

6.2.22.1 Patients Reported Outcome Measurement Information Systems – Fibromyalgia (PROMIS$_{FM}$) Fatigue Profile

The PROMIS$_{FM}$ fatigue profile is a 16-question instrument in a 5-point numeric rating scale (1 to 5; where 1 corresponds to 'Not at all', 2 corresponds to 'A little bit', 3 corresponds to 'Somewhat', 4 corresponds to 'Quite a bit', 5 correspond to 'Very much') that examines the fatigue experience and intensity of impact of fatigue in social, cognitive, and motivation subdomains. Scoring is done by calculating raw scores for each subdomain by summing subject's answers. Missing values are not allowed and if any data missing for a domain then total raw score will not be calculated. After raw scores are calculated a scoring table will be used to translate the total raw score into a T-score for each subject.

6.2.22.2 Patients Reported Outcome Measurement Information Systems (PROMIS) Sleep Disturbance

The PROMIS sleep disturbance is an 8-question instrument in a 5-point numeric rating scale (1 to 5; where 1 corresponds to 'Not at all', 2 corresponds to 'A little bit', 3 corresponds to 'Somewhat', 4 corresponds to 'Quite a bit', 5 correspond to 'Very much') that assesses sleep disturbance in subjects 18 years and older. Scoring is done by calculating total raw scores for each domain by summing subject's answers. Missing values are not allowed and if any data missing for a domain then total raw score will not be calculated. After raw scores are calculated a scoring table will be used to translate the total raw score into a T-score for each subject.

6.2.22.3 Patients Reported Outcome Measurement Information Systems (PROMIS) Physical Function

The PROMIS sleep disturbance is an 12-question instrument in a 5-point numeric rating scale (1 to 5; where 1 corresponds to 'Unable to do', 2 corresponds to 'With much difficulty', 3 corresponds to 'With some difficulty', 4 corresponds to 'With a little difficulty', 5 correspond to 'Without any difficulty') that measures the self-reported performance of physical activities among fibromyalgia patients. If subject answered 'YES' in the first question 'Can you walk 25 feet on a level surface

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[redacted]

(with or without support)?', then he/she filled all the following 12 questions. If subject answered 'NO' then only 6 further questions were filled. Scoring is done by calculating total raw scores for each domain by summing subject's answers. Missing values are not allowed and if any data missing for a domain then total raw score will not be calculated. After raw scores are calculated a scoring table will be used to translate the total raw score into a T-score for each subject.

6.2.23 [redacted]

[redacted]

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. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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.

[redacted]

[redacted]

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) 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.

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 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.

P-values will be quoted to 3 decimal places. 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.

[redacted]

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

Treatment group labels will be displayed as follows:

NYX-2925 50 mg (N=XX)	NYX-2925 100 mg (N=XX)	Placebo (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:

- 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, for all subjects
- The number of subjects who were randomized in error and received no IMP will be summarized overall
- The number of subjects who failed screening and the reasons for failure will be tabulated for all subjects
- The number of early withdrawals and the reasons for withdrawal will be tabulated by treatment group and overall, for the Screened Population
- 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

The comparability of treatment group with respect to subject demographics and baseline characteristics will be assessed in a descriptive manner.

[redacted]

[redacted]

Standard continuous or categorical variable summaries will be presented by randomized treatment group for the following variables based on the Safety Population.

- Age (years)
- Sex (male/female)
- Fertility status (for female subjects only)
- Ethnicity
- Race
- Height (cm), weight (kg), BMI (kg/m^2)
- Physical and neurological examination (Normal/Abnormal, Not Clinically Significant [NCS], Abnormal, Clinically Significant [CS]) by body system at screening

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. Conditions will be presented by Medical Dictionary of Regulated Activities (MedDRA) Version 24.1 primary system organ class and preferred term.

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.

6.9 Exposure to Study Drug

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

6.10 Treatment Compliance

Treatment compliance, calculated as defined in Section 6.2.8, 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

[redacted]

6.11 Efficacy Analyses

All statistical tests will be performed using a one-tailed 5% overall significance level as primary analysis. All comparisons between treatments will be reported with one-sided 95% confidence intervals (CI). All analyses will be performed independently on the treatment groups.

All statistical tests will be repeated using a two-sided 5% overall significance level, unless otherwise stated. All comparisons between treatments will be also reported with two-sided 95% CI.

6.11.1 Primary Endpoint

The primary efficacy endpoint is the change from baseline to Week 12 in the weekly mean of the daily NRS score assessing average pain intensity in the past 24 hours. The hypothesis for one-sided testing between NYX-2925 50mg- and placebo- treated groups is as follows:

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

The hypothesis for testing between NYX-2925 100 mg- and placebo- treated groups is as follows:

$$H_0 = \mu_{NYX,100\,mg} - \mu_{placebo} \geq 0 \qquad \text{versus} \qquad H_1 = \mu_{NYX,100mg} - \mu_{placebo} < 0$$

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, $\mu_{NYX,100\,mg}$ denotes the mean change from baseline to Week 12 in the weekly mean of the NRS score in the NYX-2925 100 mg treatment group and $\mu_{NYX,placebo}$ denotes the mean change from baseline to Week 12 in the weekly mean of the NRS score in the placebo group.

The hypothesis for two-sided testing between NYX-2925 50mg- and placebo- treated groups is as follows:

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

The hypothesis for testing between NYX-2925 100 mg- and placebo- treated groups is as follows:

$$H_0 = \mu_{NYX,100\,mg} - \mu_{placebo} = 0 \qquad \text{versus} \qquad H_1 = \mu_{NYX,100mg} - \mu_{placebo} \neq 0$$

[redacted]

6.11.1.1 Estimand

The primary efficacy analysis will evaluate the treatment-policy estimand to estimate the improvement (reduction) from Baseline in the weekly mean of the daily NRS score in subjects in the modified ITT population not discontinuing treatment early due to an AE or lack of efficacy through Week 12.

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

- 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.
- Subject-level outcome = Change from baseline in the weekly mean of the daily NRS score assessing average pain intensity in the past 24 hours
- 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. For the analysis, baseline Observation Carried Forward (BLOCF) imputation will be used to impute data for visits after a patient has discontinued randomized treatment due to either of these reasons (even if data is present).
- 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 each dose of NYX-2925 to placebo.

Any missing data at Week 12 that are not preceded by an intercurrent event (i.e., discontinuation of study drug due to AE or lack of efficacy) will remain as missing.

6.11.2 Primary Efficacy Analysis

A one-tailed restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) with one sided 95% CI will be utilized to assess the difference between treatment groups with respect to change from baseline to Week 12 in the weekly mean of the NRS score assessing average pain intensity 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

[redacted]

[redacted]

Fisher scoring algorithm (via the SCORING option of the PROC MIXED statement) will be used to obtain the initial values of covariance parameters, otherwise, no-diagonal factor analytic structure (via the TYPE = FA0(T) option of the REPEATED statement) will be used as another option. When the above strategy fails, the successive univariate regression method will be applied. The Kenward-Roger degrees of freedom correction will also be used for this analysis.

The estimate of the difference between NYX-2925 50 mg versus placebo and NYX-2925 100 mg versus placebo 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 groups. The LS means, corresponding SEs, and 95% CI for each treatment group, the treatment difference of LS means, corresponding SEs, 1-sided 95% CI and 1-sided p-value at each week will be presented. The upper limit of the 95% CI of treatment difference will be extracted using ALPHA=0.10 statement for the bound in the unfavorable direction, and the limit in the favorable direction will be set to negative infinity.

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

```
PROC MIXED DATA= DATAIN;
CLASS USUBJID TREATMENT WEEK SITE;
MODEL CHG = TREATMENT WEEK SITE TREATMENT*WEEK BASELINE / DDFM=KR;
REPEATED WEEK / SUBJECT=USUBJID TYPE=UN;
* extract two-sided 95%CI of LS MEANS each treatment groups by week;
LSMEANS TREATMENT*WEEK / DIFF CL;
* extract one-sided 95%CI of LS MEANS each treatment groups by week;
LSMEANS TREATMENT*WEEK / DIFF CL ALPHA=0.10;
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. The two-sided testing will be also performed for primary efficacy analysis and all following sensitivity analyses. The LS means, corresponding SEs, and 95% CI for each treatment group, the treatment difference of LS means, corresponding SEs, 2-sided 95% CI and 2-sided p-value at each week will be presented.

6.11.3 Sensitivity Analysis

6.11.3.1 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 will be

[redacted]

[redacted]

imputed under a missing at random (MAR) assumption while the monotone missing data will imputed under a 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 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 MAR 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.

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;
```

[redacted]

```
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:

```
PROC MIXED DATA= IMPUTED ALL;
BY  IMPUTATION ;  /* 20 sets of results produced */
CLASS USUBJID SITE TREATMENT WEEK;
MODEL CFB = TREATMENT WEEK SITE TREATMENT*WEEK BASELINE / DDFM=KR;
REPEATED WEEK / SUBJECT=USUBJID TYPE=UN;
* extract two-sided 95%CI of LS MEANS each treatment groups by week;
LSMEANS TREATMENT*WEEK / DIFF CL;
* extract one-sided 95%CI of LS MEANS each treatment groups by week;
LSMEANS TREATMENT*WEEK / DIFF CL ALPHA=0.10;
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 _IMPUTATION_ TREATMENT WEEK; 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 combined analysis of multiple imputed datasets will be presented for each week alongside the estimate of the treatment difference, SE, one-sided CIs and p-values.

6.11.3.2 Tipping Point Analysis

If the primary efficacy analysis in Section 6.11.2 significantly favors any NYX-2925 treatment group, a tipping point sensitivity analysis[4] for the primary efficacy endpoint will be conducted to investigate how severe 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 groups follows a MNAR pattern. A tipping point-based approach will be used such that the trajectories of the subjects in the NYX-2925 groups 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 0.5 (i.e., 1.0, 1.5, 2.0) 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 groups who discontinued early would need to be worse (compared to those who did not discontinue) at each post-discontinuation visit in order for the null hypothesis of no treatment difference to no longer be rejected. Intercurrent events will be imputed by BLOCF as estimand in Section 6.11.1.1. 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 groups 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 6.11.2.

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 a 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.

6.11.3.3 Supportive Analysis

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

To assess the robustness of the result observed for the primary endpoint, the one-sided 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:

```
PROC MIXED DATA= DATAIN;
CLASS TREATMENT SITE;
MODEL CFB WEEK12 = TREATMENT SITE BASELINE / SOLUTION;
* extract two-sided 95%CI of LS MEANS each treatment groups by week;
LSMEANS TREATMENT / CL DIFF;
* extract one-sided 95%CI of LS MEANS each treatment groups by week;
LSMEANS TREATMENT / CL DIFF ALPHA=0.10;
RUN;
```

The LS means, SEs, and 95% CIs will be provided for each treatment group at all weeks alongside treatment difference estimates, SE, and one-sided CIs and p-values

6.11.3.3.2 Pooled Analysis

To provide supportive evidence for the primary objective, a pooled analysis will be performed where the NYX-2925 50 mg group will be pooled with the NYX-2925 100 mg group and compared against the placebo group. The REML-based MMRM model in Section 6.11.2 will be repeated with site, treatment group (NYX-2925-treated group versus Placebo-treated group), week, baseline NRS score, and treatment-by-week interaction as terms in the model. A line plot showing the LS means and 95% CIs of the weekly mean NRS scores from Week 1 through Week 12 for pooled treatment group and placebo group will be presented.

[redacted]

6.11.3.4 [redacted]

[redacted]

[redacted]

[redacted]

6.11.4 Secondary Endpoints

All secondary endpoints will be analyzed by one-sided testing using the mITT population. The two-sided testing will be also performed for all secondary endpoints, unless otherwise stated.

6.11.4.1 Percentage of Subjects "much improved" or "very much improved" on the Patient Global Impression of Change (PGI-C) at Week 12

Analysis will utilize the one-sided Chi-square test to compare the risk between treatment groups, using the following SAS code:

```
PROC FREQ DATA= DATAIN ORDER=DATA;
TABLES TREATMENT*RESP / riskdiff (column=2 method=wald equal var=null)
ALPHA=0.10;
ODS OUTPUT PDIFFCLS = DIFF1 PDIFFTEST = PVAL1;
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 50 mg vs placebo and NYX-2925 100 mg vs placebo, the corresponding 1-sided 95% CI and 1-sided p-value for the Chi Square statistic will also be provided by visit. The lower limit of the 95% one-sided CI for the risk difference will be extracted as the lower limit of the 90% two-sided CI using the ALPHA=0.10 option with the upper limit being set to positive infinity. 2-sided Chi Square test will be performed as well with the risk difference, corresponding 2-sided 95% CI and 2-sided p-value.

[redacted]

[redacted]

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.

The analysis will be repeated for Week 4 and Week 8. Observed scores will also 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, 1-sided 95% CI and 1-sided p-value.

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

The analysis will be repeated for Weeks 4, 8, and 12 and observed value of PGI-C, and number and percentage of subjects 'much improved' or 'very much improved' on PGI-C will be presented.

6.11.4.2 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 DSIS scores at baseline and at each week, as well as the change from baseline DSIS 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, one-sided 95% CI, and one-sided p-value of the treatment difference at Week 12 will be presented. The two-sided testing will also be performed.

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

The number and percentage of subjects achieving ≥30% and ≥50% reduction from baseline in the weekly mean NRS will be analyzed using the Cochran-Mantel-Haenszel method and presented as described in Section 6.11.4.1.

[redacted]

[redacted]

6.11.4.4 Change from Baseline in the Fibromyalgia Impact Questionnaire – Revised (FIQR) score

A similar approach in modeling the REML-based MMRM as in the primary analysis will be applied to the change from baseline in the Fibromyalgia Impact Questionnaire-Revised (FIQR) total score at Week 12 except that the outcome variable will be change from baseline in the weekly mean of the FIQR total scores at Weeks 1 through 12, and the fixed effects are as follows: site, treatment group, week, baseline FIQR total score, and treatment-by-week interaction as terms in the model. Observed FIQR total scores and subscores at baseline, Week 4, Week 8 and Week 12, as well as the change from baseline FIQR total scores and subscores at each visit will be presented by treatment group. The LS means, corresponding SEs, and 95% CIs for each treatment group will also be presented. Additionally, the estimate, corresponding SE, one-sided 95% CI, and one-sided p-value of the treatment difference at Week 12 will be presented. The two-sided testing will also be performed.

6.11.4.5 Change from Baseline in the Patient Reported Outcomes Measurement Information System (PROMIS) sleep disturbance score

A similar approach in modeling the REML-based MMRM as in the primary analysis will be applied to the change from baseline in the PROMIS sleep disturbance score at Week 4, Week 8, and Week 12 except that the outcome variable will be change from baseline in the weekly mean of the PROMIS sleep disturbance score, and the fixed effects are as follows: site, treatment group, week, baseline PROMIS sleep disturbance T-score, and treatment-by-week interaction as terms in the model. Observed PROMIS sleep disturbance score at baseline, Week 4, Week 8, and Week 12, as well as the change from baseline will be presented by treatment groups. The LS means, corresponding SEs, and 95% CIs for each treatment group will also be presented at each week. Additionally, the estimate, corresponding SE, one -sided 95% CI, and one -sided p-value of the treatment difference at Week 12 will be presented. The two-sided testing will also be performed.

6.11.4.6 Change from Baseline to Week 12 in the Patient Reported Outcomes Measurement Information System – Fibromyalgia (PROMIS$_{FM}$) fatigue profile score

A similar approach in modeling the REML-based MMRM as in the primary analysis will be applied to the change from baseline in each PROMIS$_{FM}$ fatigue profile subscore at Week 4, Week 8, and Week 12 except that the outcome variable will be change from baseline in the weekly mean of the PROMIS$_{FM}$ fatigue profile subscore, and the fixed effects are as follows: site, treatment

[redacted]

[redacted]

group, week, baseline PROMIS$_{FM}$ fatigue profile subscore, and treatment-by-week interaction as terms in the model. Observed PROMIS$_{FM}$ fatigue profile subscore at baseline, Week 4, Week 8, and Week 12, as well as the change from baseline 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, one-sided 95% CI, and one-sided p-value of the treatment difference at Week 12 will be presented. The two-sided testing will also be performed.

6.11.4.7 Change from Baseline to Week 12 in the Patient Reported Outcomes Measurement Information System (PROMIS) physical function score

A similar approach in modeling the REML-based MMRM as in the primary analysis will be applied to the change from baseline in the PROMIS physical function T-score at Week 4, Week 8, and Week 12 except that the outcome variable will be change from baseline in the weekly mean of the PROMIS physical function score, and the fixed effects are as follows: site, treatment group, week, baseline PROMIS physical function score, and treatment-by-week interaction as terms in the model. Observed PROMIS fatigue profile score at baseline, Week 4, Week 8, and Week 12, as well as the change from baseline 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, one-sided 95% CI, and one-sided p-value of the treatment difference at Week 12 will be presented. The two-sided testing will also be performed.

6.11.4.8 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 the percent reduction from baseline in the weekly mean NRS average pain intensity at Week 12. Subjects 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). Patients with a worsening in the weekly mean NRS score will be categorized as having a 0% improvement. A cumulative response curve will be generated in which the response level is on the x-axis (-50% to 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

[redacted]

if two samples of data are from the same distribution. The D statistic and 1-sided p-value will be provided. The Kolmogorov-Smirnov test will be performed using the D option in PROC NPAR1WAY in SAS:

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

6.11.4.9 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 one-sided Chi-square test on equality of two proportions will be performed to compare the treatment groups. The difference in proportion with 95% CI of 1-sided testing will be provided. The SAS code will be as following:

```
PROC FREQ DATA=DATAIN;
TABLES TRT01PN*RMUSE/ RISKDIFF(EQUAL VAR=NULL CL=WALD) ALPHA=0.10;
ODS OUTPUT PDIFFCLS = DIFF1 PDIFFTEST = PVAL1;
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 week. Additionally, estimate, corresponding SE, and p-value of the treatment difference at each week will also be presented.

[redacted]

6.11.5 Other Efficacy Endpoints

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.11.6 Multiplicity

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

6.12 Safety Analyses

The safety analyses will be presented by the treatment received for the Safety Population.

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

[redacted]

[redacted]

- 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)
- 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.

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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 0.

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

All vital signs measurements throughout the study will be listed.

6.12.4 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.

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6.12.5 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.

6.12.6 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

- Changing analyses of efficacy from 2-sided testing to 1-sided testing.
- The Patient Reported Outcomes Measurement Information System – Fibromyalgia ($PROMIS_{FM}$) physical function score is updated to Patient Reported Outcomes Measurement Information System (PROMIS) physical function score, and Patient Reported Outcomes Measurement Information System – Fibromyalgia ($PROMIS_{FM}$) sleep disturbance score is updated to Patient Reported Outcomes Measurement Information System ($PROMIS_{)}$ sleep disturbance score.
- Changing the primary efficacy endpoint from 'change from baseline in the weekly mean of the daily Numerical Rating Scale (NRS) score assessing average pain intensity related to fibromyalgia in the past 24 hours' to 'change from baseline to Week 12 in the weekly

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mean of the daily Numerical Rating Scale (NRS) score assessing average pain intensity related to fibromyalgia in the past 24 hours'.

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10 REFERENCES

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2. Kratz AL, Schilling S, Goesling J, Williams DA. The PROMIS Fatigue^{FM} Profile: a self-report measure of fatigue for use in fibromyalgia. Qual Life Res. 2016 Jul;25(7):1803-13.
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6. 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 eCTD. The eCTD section is shown in bold. The following validation methods maybe used

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

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	
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14.1.1.3	Protocol Deviations - Safety Population	IP	
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14.1.3.5	Patient Global Impression of Severity at Baseline - Safety Population	IP	
14.1.3.6	Physical Examination at Baseline - Safety Population	IP	
14.1.3.7	Neurological Examination at Baseline - Safety Population	IP	
14.2	**Efficacy Analysis – 1-Sided Test**		
14.2.1	**Primary Efficacy Endpoint**		

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14.2.1.1.1	Primary Endpoint: Change from Baseline to until Week 12 in Weekly Mean NRS Score, Mixed Model for Repeated Measures – 1-Sided Test - Modified Intent-to-Treat Population	Stat IP	
14.2.1.1.2	Primary Endpoint: Change from Baseline to until Week 12 in Weekly Mean NRS Score, Mixed Model for Repeated Measures – 2-Sided Test - Modified Intent-to-Treat Population	Stat IP	14.2.1.1.1
14.2.1.2.1	Sensitivity Analysis (1): Change from Baseline to until Week 12 in Weekly Mean NRS Score, Pattern-Mixture Model – 1-Sided Test - Modified Intent-to-Treat Population	Stat IP	
14.2.1.2.2	Sensitivity Analysis (1): Change from Baseline to until Week 12 in Weekly Mean NRS Score, Pattern-Mixture Model – 2-Sided Test - Modified Intent-to-Treat Population	Stat IP	14.2.1.2.1
14.2.1.3.1	Sensitivity Analysis (2): Change from Baseline in Weekly Mean NRS score at Week 12, Tipping Point Analysis – 1-Sided Test - Modified Intent-to-Treat Population	Stat IP	
14.2.1.3.2	Sensitivity Analysis (2): Change from Baseline in Weekly Mean NRS score at Week 12, Tipping Point Analysis – 2-Sided Test - Modified Intent-to-Treat Population	Stat IP	14.2.1.3.1
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14.2.1.5.1	Pooled Analysis: Change from Baseline to until Week 12 in Weekly Mean NRS Score, Mixed Model for Repeated Measures – 1-Sided Test - Modified Intent-to-Treat Population	Stat IP	
14.2.1.5.2	Pooled Analysis: Change from Baseline to until Week 12 in Weekly Mean NRS Score, Mixed Model for Repeated Measures – 2-Sided Test - Modified Intent-to-Treat Population	Stat IP	14.2.1.5.1
14.2.1.6.1	Exploratory Analysis: Change from Baseline to until Week 12 in Weekly Mean NRS Score, By Baseline NRS Score, Mixed Model for Repeated Measures - 1-Sided Test - Modified Intent-to-Treat Population	Stat IP	14.2.1.1.1
14.2.1.6.2	Exploratory Analysis: Change from Baseline to until Week 12 in Weekly Mean NRS Score, By Baseline NRS Score, Mixed Model for Repeated Measures - 2-Sided Test - Modified Intent-to-Treat Population	Stat IP	14.2.1.1.1

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14.2.1.7.1	Exploratory Analysis: Change from Baseline to until Week 12 in Weekly Mean NRS Score, By Baseline DSIS Score, Mixed Model for Repeated Measures – 1-Sided Test - Modified Intent-to-Treat Population	Stat IP	14.2.1.1.1
14.2.1.7.2	Exploratory Analysis: Change from Baseline to until Week 12 in Weekly Mean NRS Score, By Baseline DSIS Score, Mixed Model for Repeated Measures – 2-Sided Test - Modified Intent-to-Treat Population	Stat IP	14.2.1.1.1
14.2.1.8.1	Exploratory Analysis: Change from Baseline to until Week 12 in Weekly Mean NRS Score, By Baseline $PROMIS_{FM}$ Fatigue Profile Score, Mixed Model for Repeated Measures – 1-Sided Test - Modified Intent-to-Treat Population	Stat IP	14.2.1.1.1
14.2.1.8.2	Exploratory Analysis: Change from Baseline to until Week 12 in Weekly Mean NRS Score, By Baseline $PROMIS_{FM}$ Fatigue Profile Score, Mixed Model for Repeated Measures – 2-Sided Test - Modified Intent-to-Treat Population	Stat IP	14.2.1.1.1
14.2.1.9.1	Exploratory Analysis: Change from Baseline to until Week 12 in Weekly Mean NRS Score, By Baseline PROMIS Physical Function Score, Mixed Model for Repeated Measures – 1-Sided Test - Modified Intent-to-Treat Population	Stat IP	14.2.1.1.1
14.2.1.9.2	Exploratory Analysis: Change from Baseline to until Week 12 in Weekly Mean NRS Score, By Baseline PROMIS Physical Function Score, Mixed Model for Repeated Measures – 2-Sided Test - Modified Intent-to-Treat Population	Stat IP	14.2.1.1.1
14.2.1.10.1	Exploratory Analysis: Change from Baseline to until Week 12 in Weekly Mean NRS Score, By Baseline PROMIS Sleep Disturbance Score, Mixed Model for Repeated Measures – 1-Sided Test - Modified Intent-to-Treat Population	Stat IP	14.2.1.1.1
14.2.1.10.2	Exploratory Analysis: Change from Baseline to until Week 12 in Weekly Mean NRS Score, By Baseline PROMIS Sleep Disturbance Score, Mixed Model for Repeated Measures – 2-Sided Test - Modified Intent-to-Treat Population	Stat IP	14.2.1.1.1
14.2.1.11.1	Exploratory Analysis: Change from Baseline to until Week 12 in Weekly Mean NRS Score, By Baseline HADS Depression Subscale, Mixed Model for Repeated Measures – 1-Sided Test - Modified Intent-to-Treat Population	Stat IP	14.2.1.1.1
14.2.1.11.2	Exploratory Analysis: Change from Baseline to until Week 12 in Weekly Mean NRS Score, By Baseline HADS Depression Subscale, Mixed Model for Repeated Measures – 2-Sided Test - Modified Intent-to-Treat Population	Stat IP	14.2.1.1.1

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14.2.1.12.1	Exploratory Analysis: Change from Baseline to until Week 12 in Weekly Mean NRS Score, By Baseline HADS Anxiety Subscale, Mixed Model for Repeated Measures – 1-Sided Test - Modified Intent-to-Treat Population	Stat IP	14.2.1.1.1
14.2.1.12.2	Exploratory Analysis: Change from Baseline to until Week 12 in Weekly Mean NRS Score, By Baseline HADS Anxiety Subscale, Mixed Model for Repeated Measures – 2-Sided Test - Modified Intent-to-Treat Population	Stat IP	14.2.1.1.1
14.2.1.13.1	Subgroup Analysis: Change from Baseline to until Week 12 in Weekly Mean NRS Score, By Baseline NRS Score, Mixed Model for Repeated Measures – 1-Sided Test - Modified Intent-to-Treat Population	Stat IP	14.2.1.1.1
14.2.1.13.2	Subgroup Analysis: Change from Baseline to until Week 12 in Weekly Mean NRS Score, By Baseline NRS Score, Mixed Model for Repeated Measures – 2-Sided Test - Modified Intent-to-Treat Population	Stat IP	14.2.1.1.1
14.2.1.14.1	Subgroup Analysis: Change from Baseline to until Week 12 in Weekly Mean NRS Score, By Prior Analgesic Use, Mixed Model for Repeated Measures – 1-Sided Test - Modified Intent-to-Treat Population	Stat IP	14.2.1.1.1
14.2.1.14.2	Subgroup Analysis: Change from Baseline to until Week 12 in Weekly Mean NRS Score, By Prior Analgesic Use, Mixed Model for Repeated Measures – 2-Sided Test - Modified Intent-to-Treat Population	Stat IP	14.2.1.1.1
14.2.1.15.1	Subgroup Analysis: Change from Baseline to until Week 12 in Weekly Mean NRS Score, By Subject Sourced via AES, Mixed Model for Repeated Measures – 1-Sided Test - Modified Intent-to-Treat Population	Stat IP	14.2.1.1.1
14.2.1.15.2	Subgroup Analysis: Change from Baseline to until Week 12 in Weekly Mean NRS Score, By Subject Sourced via AES, Mixed Model for Repeated Measures – 2-Sided Test - Modified Intent-to-Treat Population	Stat IP	14.2.1.1.1
14.2.1.16.1	Subgroup Analysis: Change from Baseline to until Week 12 in Weekly Mean NRS Score, By Sourced via AES and with Baseline NRS Score ≥ 5.0 versus Otherwise, Mixed Model for Repeated Measures – 1-Sided Test – Modified Intent-to-Treat Population	Stat IP	14.2.1.1.1
14.2.1.16.2	Subgroup Analysis: Change from Baseline to until Week 12 in Weekly Mean NRS Score, By Sourced via AES and with Baseline NRS Score ≥ 5.0 versus Otherwise, Mixed Model for Repeated Measures – 2-Sided Test – Modified Intent-to-Treat Population	Stat IP	14.2.1.1.1

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14.2.1.17.1	Subgroup Analysis: Change from Baseline to until Week 12 in Weekly Mean NRS Score, By Time since Diagnosed Fibromyalgia ≥ Mean versus Otherwise, Mixed Model for Repeated Measures – 1-Sided Test – Modified Intent-to-Treat Population	Stat IP	14.2.1.1.1
14.2.1.17.2	Subgroup Analysis: Change from Baseline to until Week 12 in Weekly Mean NRS Score, By Time since Diagnosed Fibromyalgia ≥ Mean versus Otherwise, Mixed Model for Repeated Measures –2-Sided Test – Modified Intent-to-Treat Population	Stat IP	14.2.1.1.1
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14.2.2.1.2	Patient Global Impression of Change, Percentage of Subjects 'Much Improved' or 'Very Much Improved' by Visit, Chi-Square Test – 2-Sided Test - Modified Intent-to-Treat Population	IP	14.2.2.1.1
14.2.2.2.1	Patient Global Impression of Change, Change from Baseline to until Week 12, Mixed Model for Repeated Measures – 1-Sided Test – Modified Intent-to-Treat Population	Stat IP	14.2.1.1.1
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14.2.2.4.1	Percentage of Subjects Achieving ≥30% Reduction or ≥50% Reduction in Weekly Mean NRS Score at Week 12, Chi-Square Test – 1-Sided Test – Modified Intent-to-Treat Population	IP	
14.2.2.4.2	Percentage of Subjects Achieving ≥30% Reduction or ≥50% Reduction in Weekly Mean NRS Score at Week 12, Chi-Square Test – 2-Sided Test – Modified Intent-to-Treat Population	IP	14.2.2.4.1
14.2.2.5.1	Fibromyalgia Impact Questionnaire – Revised (FIQR) Scores, Change from Baseline to until Week 12, Mixed model for Repeated Measures – 1-Sided Test – Modified Intent-to-Treat Population	Stat IP	

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14.2.2.5.2	Fibromyalgia Impact Questionnaire – Revised (FIQR) Scores, Change from Baseline to until Week 12, Mixed model for Repeated Measures – 2-Sided Test – Modified Intent-to-Treat Population	Stat IP	14.2.2.5.1
14.2.2.6.1	Patient Reported Outcome Measurement Information System – Fibromyalgia ($PROMIS_{FM}$) Fatigue Profile Score, Change from Baseline to until Week 12, Mixed model for Repeated Measures – 1-Sided Test – Modified Intent-to-Treat Population	Stat IP	
14.2.2.6.2	Patient Reported Outcome Measurement Information System – Fibromyalgia ($PROMIS_{FM}$) Fatigue Profile Score, Change from Baseline to until Week 12, Mixed model for Repeated Measures –2-Sided Test – Modified Intent-to-Treat Population	Stat IP	
14.2.2.7.1	Patient Reported Outcome Measurement Information System (PROMIS) Sleep Disturbance Score, Change from Baseline to until Week 12, Mixed model for Repeated Measures – 1-Sided Test – Modified Intent-to-Treat Population	Stat IP	14.2.1.1.1
14.2.2.7.2	Patient Reported Outcome Measurement Information System (PROMIS) Sleep Disturbance Score, Change from Baseline to until Week 12, Mixed model for Repeated Measures – 2-Sided Test – Modified Intent-to-Treat Population	Stat IP	14.2.1.1.1
14.2.2.8.1	Patient Reported Outcome Measurement Information System (PROMIS) Physical Function Score, Change from Baseline to until Week 12, Mixed model for Repeated Measures – 1-Sided Test – Modified Intent-to-Treat Population	Stat IP	14.2.1.1.1
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14.2.2.9.2	Average Pain Intensity, Cumulative Response in Weekly Mean NRS Score at Week 12, Kolmogorov-Smirnov Test – 1-Sided Test – Modified Intent-to-Treat Population	IP	14.2.2.9.1
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14.2.2.12.1	Proportion of Subjects Using Rescue Medication During the Study, Chi-Square Test – 1-Sided Test – Modified Intent-to-Treat Population	IP	

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14.2.3.1.2	Time in Days to First ≥30% Reduction in Weekly Mean NRS Score, Log-Rank Test –2-Sided Test – Modified Intent-to-Treat Population	IP	14.2.3.1.1
14.2.3.2.1	Average Pain Intensity Related to Fibromyalgia, Time in Days to the First ≥50% Reduction Weekly Mean NRS – 1-Sided Test – Modified Intent-to-Treat Population	IP	14.2.3.1.1
14.2.3.2.2	Average Pain Intensity Related to Fibromyalgia, Time in Days to the First ≥50% Reduction Weekly Mean NRS – 2-Sided Test – Modified Intent-to-Treat Population	IP	14.2.3.1.1
14.2.3.3.1	Hospital Anxiety and Depression Scale (HADS), Change in Subscale Score from Baseline to until Week 12, Mixed model for Repeated Measures – 1-Sided Test – Modified Intent-to-Treat Population	IP	14.2.1.1.1
14.2.3.3.2	Hospital Anxiety and Depression Scale (HADS), Change in Subscale Score from Baseline to until Week 12, Mixed model for Repeated Measures – 2-Sided Test – Modified Intent-to-Treat Population	IP	14.2.1.1.1
14.2.3.4.1	Average Pain Intensity Related to Fibromyalgia, Percentage of Subjects Achieving ≥30% Reduction or ≥50% Reduction in Weekly Mean NRS Score from Baseline to until Week 12, Chi-Square Test – 1-Sided Test – Modified Intent-to-Treat Population	IP	14.2.2.3.1
14.2.3.4.2	Average Pain Intensity Related to Fibromyalgia, Percentage of Subjects Achieving ≥30% Reduction or ≥50% Reduction in Weekly Mean NRS Score from Baseline to until Week 12, Chi-Square Test – 2-Sided Test – Modified Intent-to-Treat Population	IP	14.2.2.3.1
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14.3.5.2	Compliance with Study Drug – Safety Population	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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14.3.7.8	Concomitants Medications by ATC Level 3 and Preferred Name – Safety Population	IP	

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Figure Number	Figure Title	Validation Method	Shell Number (if repeat)
14.2.1.1	Average Pain Intensity Related to Fibromyalgia, Change from Baseline in Weekly Mean NRS Score, LS Mean (95% CI) –Line Plot – Modified Intent-to-Treat Population	MR	
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14.2.1.4	Average Pain Intensity Related to Fibromyalgia, Weekly Mean NRS Score at Week 12 Versus Baseline NRS Score – Exploratory Analyses – Scatter Plot – Modified Intent-to-Treat Population	MR	
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14.2.1.6.1	Average Pain Intensity Related to Fibromyalgia, Percent Change from Baseline of Weekly Mean NRS Score at Week 12 Versus $PROMIS_{FM}$ Fatigue Profile Experience Subscore at Baseline, Exploratory Analyses – Scatter Plot– Modified Intent-to-Treat Population	MR	14.2.1.3
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14.2.1.6.4	Average Pain Intensity Related to Fibromyalgia, Percent Change from Baseline of Weekly Mean NRS Score at	MR	14.2.1.3

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Figure Number	Figure Title	Validation Method	Shell Number (if repeat)
	Week 12 Versus PROMIS$_{FM}$ Fatigue Profile Motivation Subscore at Baseline, Exploratory Analyses – Scatter Plot– Modified Intent-to-Treat Population		
14.2.1.7	Average Pain Intensity Related to Fibromyalgia, Percent Change from Baseline of Weekly Mean NRS Score at Week 12 Versus PROMIS Sleep Disturbance Score at Baseline, Exploratory Analyses – Scatter Plot– Modified Intent-to-Treat Population	MR	14.2.1.3
14.2.1.8	Average Pain Intensity Related to Fibromyalgia, Percent Change from Baseline of Weekly Mean NRS Score at Week 12 Versus PROMIS Physical Function Score at Baseline, Exploratory Analyses – Scatter Plot– Modified Intent-to-Treat Population	MR	14.2.1.3
14.2.1.9	Average Pain Intensity Related to Fibromyalgia, Percent Change from Baseline of Weekly Mean NRS Score at Week 12 Versus HADS Depression Score at Baseline, Exploratory Analyses – Scatter Plot– Modified Intent-to-Treat Population	MR	14.2.1.3
14.2.1.10	Average Pain Intensity Related to Fibromyalgia, Percent Change from Baseline of Weekly Mean NRS Score at Week 12 Versus HADS Anxiety Score at Baseline, Exploratory Analyses – Scatter Plot– Modified Intent-to-Treat Population	MR	14.2.1.3
14.2.1.11	Average Pain Intensity Related to Fibromyalgia, Cumulative Response (Percent Reduction from Baseline) in the Weekly Mean NRS Score at Week 12, Secondary Analyses - Modified Intent-to-Treat Population	MR	
14.2.1.12	Average Pain Intensity Related to Fibromyalgia, Time to First ≥30% Reduction in Weekly Mean NRS Score – Secondary Analyses - Modified Intent-to-Treat Population	MR	
14.2.1.13	Average Pain Intensity Related to Fibromyalgia, Time to First ≥50% Reduction in Weekly Mean NRS Score – Secondary Analyses - Modified Intent-to-Treat Population	MR	14.2.1.11
14.2.1.14	Average Pain Intensity Related to Fibromyalgia, LS Mean Difference in Weekly Mean NRS Score at Week 12, 2-Sided Analyses – Forest Plot – Modified Intent-to-Treat Population	MR	14.2.1.2

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Listing Number	Listing Title	Validation Method	Shell Number (If Repeat)
16.2	**Subject Data Listings**		
16.2.1	**Discontinued Subjects**		
16.2.1.1	Subject Disposition, Early Withdrawal - Randomized Population	IP	
16.2.1.2	Subject Disposition, Screen Failures - Screened Population	IP	
16.2.1.3	Subject Disposition, Ineligible for Randomization - Screened Population	IP	
16.2.2	**Protocol Deviations**	IP	
16.2.2.1	Protocol Deviations - Screened Population	IP	
16.2.3	**Subjects Excluded from The Efficacy Analyses**	IP	
16.2.3.1	Analysis Populations - Randomized Population	IP	
16.2.4	**Demographic Data**	IP	
16.2.4.1	Demographics and Baseline Characteristics - Safety Population	IP	
16.2.4.2	Medical History - Safety Population	IP	
16.2.4.3	Inclusion and Exclusion Criteria - Safety Population	IP	
16.2.4.4	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	
16.2.5.3	Study Drug Compliance - Safety Population	IP	
16.2.5.4	Rescue Medication (Acetaminophen 500 mg) Dispensed and Returned	IP	16.2.5.2
16.2.5.5	Concomitant Medications - Safety Population	IP	
16.2.6	**Individual Efficacy Response Data**	IP	
16.2.6.1	Average Pain Intensity Related to Fibromyalgia in The Past 24 Hours - Weekly Mean NRS Score - Modified Intent-to-Treat Population	IP	
16.2.6.2	Daily Rescue Medication Usage - Modified Intent-to-Treat Population	IP	
16.2.6.3	Daily Sleep Interference Scale - Modified Intent-to-Treat Population	IP	
16.2.6.4	Fibromyalgia Impact Questionnaire – Revised Score - Modified Intent-to-Treat Population	IP	

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16.2.6.5	Patient Reported Outcomes Measurement Information System Sleep Disturbance Score - Modified Intent-to-Treat Population	IP	
16.2.6.6	Patient Reported Outcomes Measurement Information System – Fibromyalgia Fatigue Profile Score - Modified Intent-to-Treat Population	IP	
16.2.6.7	Patient Reported Outcomes Measurement Information System Physical Function Score - Modified Intent-to-Treat Population	IP	
16.2.6.8	Patient Global Impression of Severity - Modified Intent-to-Treat Population	IP	
16.2.6.9	Patient Global Impression of Change - Modified Intent-to-Treat Population	IP	
16.2.6.10	Hospital Anxiety and Depression Scale – Modified Intent-to-Treat Population		
16.2.6.11	Sheehan-Suicidality Tracking Scale - Modified Intent-to-Treat Population	IP	
16.2.6.12	Time to First ≥30% or ≥50% Reduction in Mean NRS Score for Average Pain Intensity Related to Fibromyalgia – Modified Intent-to-Treat Population	IP	
16.2.7	**Adverse Event Listings**	IP	
16.2.7.1	Adverse Event Data - Safety Population	IP	
16.2.8	**Individual Laboratory Measurements and Other Safety**	IP	
16.2.8.1	Hematology Data - Safety Population	IP	
16.2.8.2	Serum Chemistry Data - Safety Population	IP	
16.2.8.3	Urinalysis Data - Safety Population	IP	
16.2.8.4	Thyroid Panel Data - Safety Population	IP	
16.2.8.5	Serology Data - Safety Population	IP	
16.2.8.6	Vital Signs Data - Safety Population	IP	
16.2.8.7	Electrocardiogram Data - Safety Population	IP	
16.2.8.8	Physical Examination Data - Safety Population	IP	
16.2.8.9	Neurological Examination Data - Safety Population	IP	
16.2.8.10	Urine Pregnancy Testing Data - Safety Population	IP	
16.2.8.11	Urine Drug Screening Data - Safety Population	IP	

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Study Name:	A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of NYX-2925 in Subjects with Fibromyalgia
Statistical Analysis Plan (SAP) Version being approved:	NYX-2925-2005_SAP_V1.0, dated 21July2022
Tables, Figures and Listings (TFL) Shell version being approved:	NYX-2925-2005_TFL_Shells_V1.0, dated 21July2022

The above SAP / TFL Shell has been reviewed and approved by [redacted]:

Name of Author: [redacted]

Position:

Signature:

Date:

Name of Reviewer: [redacted]

Position:

Signature:

Date:

[redacted]

[redacted]

The above SAP / TFL Shell has been reviewed and approved by the Sponsor: Name of Sponsor [redacted]: Position: Signature: Date:
Name of Sponsor [redacted]: Position: Signature: Date:

[redacted]

[redacted]

Statistical Analysis Plan

Post Database Lock Addendum

Title: A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of NYX-2925 in Subjects with Fibromyalgia

Protocol Number: NYX-2925-2005

Protocol Version: Version 7.0 (Amendment 6)/ 14OCT2021

SAP Version: Version 1.0 / 21JUL2022

Addendum Version: 1.0

Addendum issue Date: 24-AUG-2022

Previous Version

Not Applicable

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1. BACKGROUND

This document details changes and / or additions to the planned statistical analyses for Aptinyx Inc, protocol NYX-2925-2005 study titled "A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of NYX-2925 in Subjects with Fibromyalgia" previously described in V1.0 of the Statistical Analysis Plan (SAP) dated 21-JUL-2022.

These amendments were made post database lock and after the study was unblinded.

Rationale for Addendum:

1) To detail the Baseline Observation Carried Forward (BLOCF) imputation used in primary efficacy analysis
2) To update the definition of prior medication
3) To update the title of outputs:

Output Number and Title	Requested Change
Table 14.2.2.2.1 Patient Global Impression of Change, Change from Baseline to until Week 12, Mixed Model for Repeated Measures – 1-Sided Test – Modified Intent-to-Treat Population	Change the title to 'Patient Global Impression of Change by Visit, Mixed Model for Repeated Measures – 1-Sided Test – Modified Intent-to-Treat Population'
Table 14.2.2.2.2 Patient Global Impression of Change, Change from Baseline to until Week 12, Mixed Model for Repeated Measures – 2-Sided Test – Modified Intent-to-Treat Population	Change the title to 'Patient Global Impression of Change by Visit, Mixed Model for Repeated Measures – 2-Sided Test – Modified Intent-to-Treat Population'

In addition to the above changes and / or additions, a number of minor changes have been made to the shells so that they reflect the presentation of the final set of tables, figures and listings (TFLs). These changes have not been detailed here.

2. CHANGES TO EXISTING SAP

2.1 Change 1

2.1.1 Original text

Section 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.

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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.

2.1.2 New text

Section 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 and 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.

2.2 Change 2

2.2.1 Original Text

Section 6.11.1.1 Estimand

The primary efficacy analysis will evaluate the treatment-policy estimand to estimate the improvement (reduction) from Baseline in the weekly mean of the daily NRS score in subjects in the modified ITT population not discontinuing treatment early due to an AE or lack of efficacy through Week 12.

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

- 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.
- Subject-level outcome = Change from baseline in the weekly mean of the daily NRS score assessing average pain intensity in the past 24 hours

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- 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. For the analysis, baseline Observation Carried Forward (BLOCF) imputation will be used to impute data for visits after a patient has discontinued randomized treatment due to either of these reasons (even if data is present).
- 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 each dose of NYX-2925 to placebo.

Any missing data at Week 12 that are not preceded by an intercurrent event (i.e., discontinuation of study drug due to AE or lack of efficacy) will remain as missing.

2.2.2 New Text

The primary efficacy analysis will evaluate the treatment-policy estimand to estimate the improvement (reduction) from Baseline in the weekly mean of the daily NRS score in subjects in the modified ITT population not discontinuing treatment early due to an AE or lack of efficacy through Week 12.

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

- 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.
- Subject-level outcome = Change from baseline in the weekly mean of the daily NRS score assessing average pain intensity in the past 24 hours
- 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. For primary efficacy analysis purposes, baseline Observation Carried Forward (BLOCF) imputation will be used to impute data for visits after a patient has discontinued randomized treatment due to either of these reasons (even if data is present).
- 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 each dose of NYX-2925 to placebo.

Any missing data at Week 12 that are not preceded by an intercurrent event (i.e., discontinuation of study drug due to AE or lack of efficacy) will remain as missing.

2.3 Change 3

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2.3.1 Original Text

Section 6.11.2 Primary Efficacy Analysis

A one-tailed restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) with one sided 95% CI will be utilized to assess the difference between treatment groups with respect to change from baseline to Week 12 in the weekly mean of the NRS score assessing average pain intensity in the past 24 hours.

2.3.2 New Text

Section 6.11.2 Primary Efficacy Analysis

A one-tailed restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) with one sided 95% CI will be utilized to assess the difference between treatment groups with respect to change from baseline to Week 12 in the weekly mean of the NRS score assessing average pain intensity in the past 24 hours. Baseline Observation Carried Forward (BLOCF) imputation (based on Section 6.11.1.1) will be used to impute data for subjects discontinuing the study drug due to an AE or lack of efficacy prior to Week 12.

2.4 Change 4

2.4.1 Original Text

Section 6.11.3.1 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 will be imputed under a missing at random (MAR) assumption while the monotone missing data will be imputed under a missing not at random (MNAR) assumption (i.e., that missingness is also dependent on the unobserved variable values).

2.4.2 New Text

Section 6.11.3.1 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 will be imputed under a missing at random (MAR) assumption while the monotone missing data and data occurring after an ICE will be imputed under a missing not at random

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(MNAR) assumption (i.e., that missingness is also dependent on the unobserved variable values).

2.5 Change 5

2.5.1 Original Text

Section 6.11.3.2 Tipping Point Analysis

If the primary efficacy analysis in Section 6.11.2 significantly favors any NYX-2925 treatment group, a tipping point sensitivity analysis[4] for the primary efficacy endpoint will be conducted to investigate how severe 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 groups follows a MNAR pattern. A tipping point-based approach will be used such that the trajectories of the subjects in the NYX-2925 groups 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 0.5 (i.e., 1.0, 1.5, 2.0) 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 groups who discontinued early would need to be worse (compared to those who did not discontinue) at each post-discontinuation visit in order for the null hypothesis of no treatment difference to no longer be rejected. Intercurrent events will be imputed by BLOCF as estimand in Section 6.11.1.1. Each imputed dataset produced through PROC MI procedure will be processed as follows.

2.5.2 New Text

Section 6.11.3.2 Tipping Point Analysis

If the primary efficacy analysis in Section 6.11.2 significantly favors any NYX-2925 treatment group, a tipping point sensitivity analysis[4] for the primary efficacy endpoint will be conducted to investigate how severe 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 and data occurring after an ICE in the NYX-2925 groups follows a MNAR pattern. A tipping point-based approach will be used such that the trajectories of the subjects in the NYX-2925 groups after early withdrawal

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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 0.5 (i.e., 1.0, 1.5, 2.0) 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 groups who discontinued early would need to be worse (compared to those who did not discontinue) 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 follow.

2.6 Change 6

2.6.1 Original Text

Section 6.11.3.3.1 Analysis of Covariance on change from baseline to Week 12 in the weekly mean of the NRS score assessing average pain intensity in the past 24 hours

To assess the robustness of the result observed for the primary endpoint, the one-sided 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.

2.6.2 New Text

Section 6.11.3.3.1 Analysis of Covariance on change from baseline to Week 12 in the weekly mean of the NRS score assessing average pain intensity in the past 24 hours

To assess the robustness of the result observed for the primary endpoint, the one-sided 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. No imputation will be performed ahead of performing this analysis.

2.7 Change 7

2.7.1 Original Text

Section 6.11.3.3.2 Pooled Analysis

To provide supportive evidence for the primary objective, a pooled analysis will be performed where the NYX-2925 50 mg group will be pooled with the NYX-2925 100 mg group and compared against the placebo group. The REML-based MMRM model in Section

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6.11.2 will be repeated with site, treatment group (NYX-2925-treated group versus Placebo-treated group), week, baseline NRS score, and treatment-by-week interaction as terms in the model. A line plot showing the LS means and 95% CIs of the weekly mean NRS scores from Week 1 through Week 12 for pooled treatment group and placebo group will be presented.

2.7.2 New Text

Section 6.11.3.3.2 Pooled Analysis

To provide supportive evidence for the primary objective, a pooled analysis will be performed where the NYX-2925 50 mg group will be pooled with the NYX-2925 100 mg group and compared against the placebo group. The REML-based MMRM model in Section 6.11.2 will be repeated with site, treatment group (NYX-2925-treated group versus Placebo-treated group), week, baseline NRS score, and treatment-by-week interaction as terms in the model. No imputation will be performed ahead of performing this analysis. A line plot showing the LS means and 95% CIs of the weekly mean NRS scores from Week 1 through Week 12 for pooled treatment group and placebo group will be presented.

2.8 Change 8

2.8.1 Original Text

Section 6.11.3.4 Exploratory Analyses

Potential moderators of treatment outcome will be explored. An MMRM model will be performed in a similar manner to the primary analysis, as described in Section 6.11.2, with fixed effects for site, sex, treatment group, week, baseline NRS score, and treatment-by-week interaction. Fixed effect terms for baseline variable of interest and treatment-by-baseline variable interaction will also be added to the model as follows (one model per point).

2.8.2 New Text

Section 6.11.3.3 Exploratory Analyses

Potential moderators of treatment outcome will be explored. An MMRM model will be performed in a similar manner to the primary analysis, as described in Section 6.11.2, with fixed effects for site, sex, treatment group, week, baseline NRS score, and treatment-by-week interaction. Fixed effect terms for baseline variable of interest and treatment-by-

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baseline variable interaction will also be added to the model as follows (one model per point). No imputation will be performed ahead of performing these exploratory analyses.

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Approval for implementation of

Statistical Analysis Plan Post Database Lock Addendum

REVIEW / APPROVAL SIGNATURES

Plan Author	**Plan Reviewer,** [redacted]
[redacted]	[redacted]
Plan Approver, [redacted]	**Plan Approver,** [redacted]
[redacted]	[redacted]

[redacted]