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NYX-2925-2002

A Phase 2, Single-Blind, Exploratory, Placebo-controlled, Pilot Study to Assess the Efficacy and Safety of Daily Oral NYX-2925 in Subjects With Fibromyalgia

SAP

November 26, 2018

Statistical Analysis Plan

A Phase 2, Single-Blind, Exploratory, Placebo-controlled, Pilot Study to Assess the Efficacy and Safety of Daily Oral NYX-2925 in Subjects with Fibromyalgia

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Prepared by:	[redacted]
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This document has been reviewed and accepted by:

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Other analyses not related to the MRI/QST analyses provided by:

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2. Introduction

This statistical analysis plan (SAP) describes the planned statistical analysis and reporting of the clinical study protocol titled "A Phase 2, Single-Blind, Exploratory, Placebo-controlled, Pilot Study to Assess the Efficacy and Safety of Daily Oral NYX-2925 in Subjects with Fibromyalgia" dated on March 7, 2018, amendment #3.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials[1]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association[2] and the Royal Statistical Society[3], for statistical practice.

The purposes of this SAP are to:

- Outline the types of analyses and presentations of data that will form the basis for drawing conclusions to the study objectives and hypotheses outlined in the protocol
- Explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices for Good Statistical Practice

All analyses described in this plan are considered *a priori* analyses in that they have been defined prior to performing any interim analyses. The planned analyses identified in this SAP may be included in clinical study reports (CSR), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned exploratory analyses performed will be clearly identified as such in the final CSR.

The following documents were reviewed in preparation of this SAP:

- [redacted]
- [redacted]
- [redacted]

- [redacted]
- [redacted]

The reader of this SAP is encouraged to also read the clinical study protocol and other identified documents for details on the planned conduct of this study. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analyses.

3. Study Objectives

3.1 Primary Objective

The primary objective of this study is to determine whether daily dosing with NYX-2925 20 or 200 mg changes the markers of central pain processing in subjects with fibromyalgia using functional magnetic resonance imaging (fMRI), resting state functional connectivity magnetic resonance imaging (rs-fcMRI) and proton magnetic resonance spectroscopy (^{1}H-MRS) on active drug versus placebo.

[redacted]

4. Study Overview

4.1 Study Design and Study Drug Treatment Periods

This is a single-blind, exploratory, placebo-controlled, pilot study to assess the efficacy and safety of daily oral NYX-2925 in fibromyalgia subjects. The study includes a screening period (up to 30 days), a placebo period, an active treatment period with 2 dose strengths, and a follow-up period as follows:

- Placebo PO QD for 2 weeks
- NYX-2925 20 mg PO QD for 2 weeks
- NYX-2925 200 mg PO QD for 2 weeks
- Follow-up for 1 week

The schedule of assessments is provided in in Appendix I.

4.2 Subject Randomization

This study does not require a randomization because the treatment periods are fixed.

4.3 Number of Subjects

The protocol for this study planned on enrolling approximately 24 subjects at 2 study sites in the United States.

4.4 Sample Size Considerations

The sample size for this pilot study was based on practical, clinical considerations rather than a formal determination of statistical power.

4.5 Unblinding Study Drug Treatment Procedures

Not applicable because this is not a double-blind or randomized study.

4.6 Analyses Changes from the Protocol

In Section 12.6.1 of the protocol, it states that TEAE summaries will be provided separately for each study period and the follow-up period. TEAEs will be summarized and grouped based on the last study drug treatment the subject received compared to the start date of the event explained in Section 5.2. The rest of the analyses stated in the protocol support the analyses planned in this SAP.

5. General Statistical Principles

5.1 Key Definitions

The following items below are standard terminologies discussed throughout the SAP.

5.1.1 Day 1/Date of First Dose

The date of first dosing of study drug is not collected on the CRF because subjects are given study drug to administer themselves. Since both compliance and missed doses were captured, it will be assumed that Day 1 is the same day as the first dosing day of study drug for subjects in the safety population later described in the SAP in Section 6.1.

5.1.2 Study Day

Study day will be calculated in reference to Day 1 stated above in Section 5.1.1. For assessments conducted on or after the Day 1 date, study day is calculated as the assessment date – Day 1 date + 1. For assessments conducted before the Day 1 date, study day is calculated as the assessment date – Day 1 date. There is no Study Day 0 in this study.

5.1.3 Not Reported

A not reported value may be displayed in a listing, summary statistics table, frequency table, shift table, etc. The not reported record could be due to a missed sample/measurement/assessment, missed visit, unable to calculate a value, or withdrawal from the study early.

5.1.4 Baseline and Post-Baseline Values

Unless otherwise specified, the baseline value is defined as the last measurement/assessment collected/derived on Day 1 or during screening. Unless otherwise specified, post-baseline values are defined as collected/derived measurements/assessments after Day 1.

For specific questionnaire assessments, missing responses on Day 1 will not be substituted for screening values for the baseline specific questionnaires. If the total score cannot be calculated at Day 1, then the screening visit will be used if the total score can be calculated at screening. If the total score cannot be calculated for both screening and Day 1 visits, then the latest individual values and subscale scores will be used for the baseline. All questions within a specific questionnaire will be paired together in an analysis visit for the baseline records.

5.1.5 Change from Baseline

If both post-baseline and baseline values are present/imputed, then change from baseline is defined as each post-baseline value – baseline value. Otherwise the change from baseline will not be reported.

5.1.6 Change from Treatment Periods

If both post-values and pre-values are present/imputed then change from treatment periods are defined as the following:

- Change from Week 2 (Placebo)
  - Post-values conducted at Weeks 3, 4, 5, 6, and Follow-up (Week 7)
  - Pre-value is defined as the last measurement/assessment collected/derived on Week 2 (end of the Placebo Period)
- Change from Week 4 (NYX-2925 20 mg PO QD)
  - Post-values conducted at Week 5, Week 6, and Follow-up (Week 7)
  - Pre-value is defined as the last measurement/assessment collected/derived on Week 4 (end of the NYX-2925 20 mg PO QD Period)
- Change from Week 6 (NYX-2925 200 mg PO QD)
  - Post-values conducted at Follow-up (Week 7)
  - Pre-value is defined as the last measurement/assessment collected/derived on Week 6 (end of the NYX-2925 200 mg PO QD Period)

Otherwise the change from treatment periods will not be reported.

5.1.7 Percent Change from Baseline

If the baseline value is not equal to zero or missing and the change from baseline value is present/imputed, then the percent change from baseline is defined as 100 x (change from baseline / baseline) and is rounded off to 1 number after the decimal point. Otherwise the percent change from baseline will not be reported.

5.2 Treatment Allocation

Subjects are planned to receive multiple study drug treatments in the study. Therefore, the following treatments will be assigned during these periods:

- Screening Visit until 1 Day Prior to the Day 1 (Baseline) Visit: No Treatment
- Day 1 (Baseline) Visit until the Week 2 Visit: [redacted]
- 1 Day After Week 2 Visit until the Week 4 Visit: [redacted]
  - If any adverse events and/or concomitant medications start on the Week 2 visit, then those records will be assigned to the [redacted] treatment arm.
- 1 Day After Week 4 Visit until the Week 6 Visit: [redacted]
  - If any adverse events and/or concomitant medications start on the Week 4 visit, then those records will be assigned to the [redacted] treatment arm.
- 1 Day After Week 6 Visit until the Follow-Up (Week 7) Visit: [redacted]
- Unscheduled or Early Termination Visits: Last Study Drug Dispensed and Taken

5.3 Treatment Group Comparisons

The following treatment groups will be summarized in the statistical tables:

- Placebo
- NYX-2925 20 mg PO QD
- NYX-2925 200 mg PO QD
- All Doses of NYX-2925
  - Pooled for adverse events, concomitant medications, and study drug treatment compliance and exposure tables.
- Not Treated
  - This will only be displayed for the analysis population table that presents subjects screened, but were not enrolled in the study or dispensed study drug.
- All Subjects
  - This will only be displayed for the analysis population and concomitant medications tables.

The following changes in treatment period comparisons will be performed for efficacy:

- Change from Baseline
- Change from Week 2 [redacted]
- Change from Week 4 [redacted]
- Change from Week 6 [redacted]

5.4 Conventions

[redacted]

5.4.1 Descriptive Statistics

Descriptive statistics (the number of subjects [n], mean, standard deviation [SD], median, minimum, maximum, and not reported) will be used to summarize continuous variables. Means will be presented to one more decimal place than the recorded data. Medians will be presented using the same number of decimal places as the recorded data unless the calculated median results in an additional decimal place ending in "5" (i.e. 5 & 7 = 6, 5 & 8 = 6.5, etc.). Standard deviations will be presented to two more decimal places than the recorded data. Minimum and maximum values will be presented using the same number of decimal places as the recorded data.

For data reporting 3 or more numbers after the decimal point (i.e. urinalysis specific gravity), the descriptive statistics for mean, standard deviation, median, minimum, and maximum will all be reported to the same precision as the data was collected. For data reporting 2 numbers after the decimal point, the descriptive statistics for standard deviation will be reported as 3 numbers after the decimal place (same as the mean).

5.4.2 Frequency Distributions

Frequency distributions (count [n], percentage of subjects [%], and not reported) will be used to summarize categorical or qualitative variables. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population for the treatment groups for that particular time point assessment. Records that are missing or not done will be displayed as "Not Reported" and will not be factored into the percentage calculation, unless otherwise specified. Percentages will be presented to a maximum of one number after the decimal place.

5.4.3 Safety Data Statistical Inference

All safety data summaries will use descriptive statistics, frequency distributions, and/or shift tables. No formal statistical testing will be performed with the safety data.

5.4.4 Efficacy and Pharmacodynamic Data Statistical Inference

5.4.4.1 P-values and Type I Error

P-values will be reported out and rounded off to 4 numbers after the decimal point (i.e. "0.####). Any p-values that are > 0.9999 will be reported as ">.9999" in the tables. Any p-values that are < 0.0001 will be reported as "<.0001" in the tables. Unless otherwise specified, p-values will be tested using alpha at the 0.05 level. This pilot study is not formally powered to test any specific hypothesis; and, that should be taken into consideration for all statistical conclusions.

5.4.4.2 Paired *t*-test and Wilcoxon Signed-Rank Test

Testing for differences between treatment periods will be performed by using a 2-sided paired *t*-test, comparing pre and post values based on the analysis visits collected for particular pharmacodynamic and efficacy data stated in Sections 9 and 10. The null hypothesis will be defined as the mean change from pre and post values is 0. Both the pre and post values must be non-missing in order to be included in the paired *t*-test comparison. Here is the SAS® code:

```
PROC TTEST DATA=ADAM;
    /* where CHG# is the specific post-value – pre-value of interest */
    VAR CHG#;
RUN;
```

Additionally, the nonparametric Wilcoxon signed-rank test will be provided along with the 2-sided paired *t*-test. The null hypothesis will be defined as the median change from pre and post values is 0. Both the pre and post values must be non-missing in order to be included in the statistical comparison. Here is the SAS® code:

```
PROC UNIVARIATE DATA=ADAM;
    /* where CHG# is the specific post-value – pre-value of interest */
    VAR CHG#;
RUN;
```

5.4.4.3 Frequency Distribution Tests

Frequency distributions that have two responses (i.e. yes/no) and compare two different treatment periods (i.e. NYX-2925 20 mg PO QD versus placebo) will use McNemar's exact test for reporting a p-value. This is referred to as a 2x2 table for dependent categorical data. Subjects will need to have both treatment period values as non-missing for the comparison. The 2x2 table must have less than 2 non-missing levels or the p-value will be considered non-calculable. Here is the SAS® code:

```
PROC FREQ DATA=ADAM;
    WEIGHT COUNT;
    /* where BEFORE and AFTER represent the 2 different treatment periods comparison */
    TABLES BEORE*AFTER / AGREE;
    EXACT MCNEM;
    ODS OUTPUT MCNEMARSTEST=MCNEMARSTEST;
RUN;
```

5.5 Analysis Visits

Analysis visits are determined based on the collected/derived data for the study that will be used for listings and statistical analyses. In some events, there may be differences in visits depending on the data used for statistical summaries and as a result analysis visits are defined. For example, data for

efficacy versus safety may have different methods for defining the analysis visits. The subsections below represent the analysis visits that will be used to support the analyses in this SAP.

In the event more than one record is collected/derived within an analysis visit, the non-missing record with the date closest to the target day will be selected. If there is a tie between two dates between the target date, then the first date will be used. If more than one non-missing record occurs on the same date, then the first planned scheduled result will be used.

Clinical laboratory tests will also consider lowest, highest, and most abnormal post-baseline results as additional analyses. More details are provided in Section 12.2.

5.5.1 Safety and Efficacy Analysis Visits

Each safety analyses section will state which analysis visits will be used in their respective summary tables. All collected/derived records will be included in the appendix listings.

Protocol/CRF Term	Analysis Visit (Target Day)	Study Day Window
Screening	Screening (-30)	≤ Day -1
Day 1/Baseline	Day 1 (1)	Only Day 1
N/A	Baseline[(a)] (N/A)	≤ Day 1
N/A	Unscheduled Week 1 (N/A)	Day 2 to Day 3
Week 1	Week 1 (7)	Day 4 to Day 10
Week 2	Week 2 (14)	Day 11 to Day 17
Week 3	Week 3 (21)	Day 18 to Day 24
Week 4	Week 4 (28)	Day 25 to Day 31
Week 5	Week 5 (35)	Day 32 to Day 38
Week 6	Week 6 (42)	Day 39 to Day 45
Follow-Up/Week 7	Early Termination[(b)] (N/A)	Day 2 or Later
Follow-Up/Week 7	Follow-Up (Week 7)[(c)] (49)	Day 46 to Day 56
N/A	Unscheduled Late Follow-Up[(d)] (Week 7) (N/A)	Day 57 or Later
N/A	Repeat Follow-Up[(e)] (N/A)	Any Repeat Follow-Up Visits
N/A	Last Post-NYX-2925 Visit[(f)] (N/A)	Week 3 Visit + 1 Day or Later
N/A	Any Post-NYX-2925 Visit[(g)] (N/A)	Week 3 Visit + 1 Day or Later
N/A	Overall Post-NYX-2925 Visits[(h)] (N/A)	Week 3 Visit + 1 Day or Later

[(a)] Baseline definition described in Section 5.1.4.

(b) The Early Termination visit will only be included in summary tables for last and overall post-NYX-2925 visits if study drug of NYX-2925 was dispensed for those particular subjects.

(c) Subjects will return to the study site 7 days following the Week 7/Early Termination visit.

(d) If subjects return for the Follow-Up (Week 7) visit after the allowed study window (≥ Day 57).

(e) If subjects return after the Follow-Up (Week 7) visit for a repeat assessment, that visit and any additional visits will be identified as a Repeat Follow-Up visit.

(f) This considers the last post-baseline values collected/derived for a particular set of data after study drug of NYX-2925 was dispensed (including unscheduled and repeated measurements/assessments).

(g) This is used for considering any worst-case, lowest, highest, etc. values for any post-baseline data after study drug of NYX-2925 was dispensed. Examples of this are used for clinical laboratory tests and C-SSRS data.

(h) This is used for combining all post-baseline data after study drug of NYX-2925 was dispensed. Examples of this are used for study drug accountability, compliance, and treatment exposure.

[redacted]

[redacted]

Protocol/CRF Term	Analysis Visit	Study Day Window
Screening	Screening(a)	≤ Day -8
Baseline	Baseline	Day -7 to Day -1
Week 1	Week 1	Day 1 to Week 1 Visit - 1
Week 2	Week 2	Week 1 Visit Day to Week 2 Visit - 1
Week 3	Week 3	Week 2 Visit Day to Week 3 Visit - 1
Week 4	Week 4	Week 3 Visit Day to Week 4 Visit - 1
Week 5	Week 5	Week 4 Visit Day to Week 5 Visit - 1
Week 6	Week 6	Week 5 Visit Day to Week 6 Visit - 1
Follow-Up/Week 7	Follow-Up (Week 7)	Week 6 Visit Day to Follow-Up Visit
N/A	After Follow-Up (Week 7)(a)	After the Follow-Up Visit

(a) Screening and after Follow-Up (Week 7) values will be displayed in listings, but not included summary tables.

5.6 Data Imputations

Standard methods described below will be used for imputing missing data and character values in numeric collected parameter data.

5.6.1 Character Values in Numeric Data

Characters such as "<, >, and/or =" may be included in some parameter data values that are supposed to be collected in a numeric format. This is most commonly seen in laboratory data. Analysis values for results with "<=" or ">=" will be analyzed with those characters stripped from the collected result (i.e. "<=1.030" = "1030" and ">=100" = "100").

Analysis values with only "<" will be handled using these methods:

- For precision data collected with at least one number after the decimal point, the analysis value will be the numeric value minus 1 extra precision unit (i.e. "<0.1" = "0.09").
- For whole numbers collected and the value reported as "<0" then the analysis value will be 0.
- For other whole numbers collected, the analysis value will be the numeric value minus 1.

Analysis values with only ">" will be handled using these methods:

- For precision data collected with at least one number after the decimal point, the analysis value will be the numeric value plus 1 extra precision unit (i.e. ">5.25" = "5.251").
- For whole numbers collected, the analysis value will be the numeric value plus 1.

For listing purposes, the collected results will be displayed in the CSR listings and appendices (i.e. "<5.0" over "4.99").

5.6.2 Missing Analysis Values

No missing analysis values will not be imputed for this study.

5.6.3 Missing or Partial Dates

Adverse Event Start Dates:

- Method 1 – Earliest Possible Start Date:
  - If any combination of the year, month, and/or day are missing then the start date will be set to the earliest possible date that is ≥ to the screening date.
- Method 2 – Latest Possible Start Date:
  - If any combination of the year, month, and/or day are missing then the start date will be set to the latest possible date that is ≤ to the latest possible adverse event end date. If the adverse event is ongoing after the final visit for the subject, then the final visit date will be used.

Prior/Concomitant Medications Start Dates:

- Method 1 – Earliest Possible Start Date:
  - If any combination of the year, month, and/or day are missing then the start date will be set to the earliest possible date that is ≥ to the subject's date of birth.
- Method 2 – Latest Possible Start Date:
  - If any combination of the year, month, and/or day are missing then the start date will be set to the latest possible date that is ≤ to the latest possible medication end date. If the medication is ongoing after the final visit for the subject, then the final visit date will be used.

Adverse Event and Prior/Concomitant Medications End Dates:

- Method 1 – Earliest Possible End Date:
  - If any combination of the year, month, and/or day are missing then the end date will be set to the earliest possible date that is ≥ to the earliest possible adverse event/medication start date.
- Method 2 – Latest Possible End Date:
  - If any combination of the year, month, and/or day are missing then the end date will be set to the latest possible date that is ≤ to the subject's final visit date. If the adverse event/medication is ongoing after the final visit for the subject, then the final visit date will be used.

Medical History Disease Onset Dates:

- If year is missing, then the date will not be imputed.
- If both the month and day are missing, then the date will be imputed as July 1st with the year collected. However, if this imputed date is ≥ to the screening date then the imputed date will be the screening date minus 1 day.
- If only the day is missing, then the date will be imputed as the 15th with the year and month collected. However, if this imputed date is ≥ to the screening date then the imputed date will be the screening date minus 1 day.

5.7 Multiplicity Adjustments

No multiplicity adjustments will be made for this study.

5.8 By-Center Analyses

No formal by-center analyses is planned for this study.

5.9 Subpopulation Analyses

No formal subpopulation analyses are planned for this study.

6. Analysis Populations

Subjects who screened for the study, but were excluded from any of the analysis populations below will have the reasons why presented in a subject listing and frequency distribution tables.

6.1 Safety Population

All subjects who were dispensed study drug during the Day 1 (Baseline) visit and did not return all the study drug in their next visit will be in the safety population. It will be assumed that these subjects in the safety population have taken at least one dose of study drug. Subjects in the safety population will be used for all analyses of safety data and will be analyzed based on the actual treatment received within each treatment period in the study.

6.2 Efficacy Population

The efficacy population will be based on subjects included in the safety population and have at least one post-baseline visit after receiving NYX-2925 20 mg PO QD. Subjects in the efficacy population will be analyzed based on the planned treatment they were supposed to receive within each treatment period. The efficacy population will be the primary analysis population used for this study.

6.3 PP Population

The Per Protocol (PP) population will be based on all subjects in the efficacy population and the following criteria:

- Subjects first received Placebo for 2 weeks, then NYX-2925 20 mg PO QD for 2 weeks, and then NYX-2925 200 mg PO QD for 2 weeks;
- Subjects received the appropriate study drug for each treatment period;
- Subjects did not use any of the prohibited concomitant medications listed in Section 8.8 of the protocol;
- Subjects who have an overall NYX-2925 study drug treatment compliance between 80% and 125%;

Subjects in the PP population will be defined based on a review of the relevant data by the Sponsor prior to database lock and subjects may be excluded due to particular major protocol deviations. Subjects in the PP population will be analyzed based on the planned treatment they were supposed to receive within each treatment period.

7. Disposition, Baseline, and Other Characteristics

All subjects will be summarized in the tables based each study treatment they were dispensed and received. The maximum strength study drug dose received, "Screen Failure" or "Not Treated" will be displayed in the subject listings.

7.1 Subject Disposition

All subjects who were screened in the study will be summarized in a frequency distribution table by their following status after the baseline visit where the denominator will be the number of subjects screened:

- Screened and Treated
- Screened and Not Treated

Any subjects "Screened and Not Treated" will be subcategorized for the following reasons collected on the CRF: does not meet inclusion/exclusion criteria, withdrew consent, adverse event, protocol non-compliance, lost to follow-up, pregnancy, sponsor terminated the study, and other. "Other" will be displayed on the tables if collected on the CRF and no other standardized term may be used.

Frequency distributions of the subjects who completed each treatment period and the overall study will be summarized. Furthermore, frequency distributions for the subjects who discontinued prematurely will be summarized along with the primary reason for withdrawal or discontinuation collected on the CRF.

The subject disposition listings will include all subjects with the following data: date informed consent signed, IRB approval date, date of completing or discontinuing from the study, date of last dose of study drug (if applicable), study completion status, and primary reason for study discontinuation (if applicable), and the date of the follow-up visit or reason why it was not done. Subjects who received study drug will have their calculated study days presented next to the dates in parentheses.

7.2 Demographics and Disease History

Demographics and baseline characteristics will be summarized for the safety, efficacy, and PP populations. Descriptive statistics will be calculated for the following continuous demographic and baseline characteristic variables at screening: age, height, weight, and body mass index (BMI). Frequency distributions will be tabulated for the following categorical demographic variables: sex, childbearing potential, race, and ethnicity. Sex will be listed and summarized in the tables even though all the subjects screened for this study are females.

The onset disease history for fibromyalgia will be summarized based on the number of years in the demographics and baseline characteristics table. The fibromyalgia event will also be provided in the medical history subject listing, but not in the summarized in the medical history table.

The number of years for fibromyalgia be calculated as the (number of days from the onset date to the latest signed informed consent date) / 365.25 rounded off by one number after the decimal point. For partial dates collected, the imputation fibromyalgia onset date described in Section 5.6.3 will be used.

Subject listings will include the subject's date of birth, any reasons why the subject does not have childbearing potential (if applicable), and all continuous/categorical variables listed above.

7.3 Subject Inclusion and Exclusion Criteria

Inclusion and exclusion criteria will be provided in a subject listing where each subject number not meeting each criterion will be displayed. The inclusion/exclusion criteria numbers not met will be listed with a brief description of the inclusion/exclusion criteria.

7.4 Medical History

Medical history data will be mapped using the Medical Dictionary for Regulatory Activities (MedDRA, version 19.0 to system organ class (SOC), and preferred term (PT). This data will be summarized in a frequency distribution. Subjects may have more than one medical history record per SOC and PT. At each level of subject summarization, a subject will be counted once if he/she reports one or more medical history record at that specific level. Subjects must have a medical history of fibromyalgia in order to be eligible for the study. Therefore, fibromyalgia will not be counted in the medical history frequency distribution table, but a footnote will be added that all subjects had fibromyalgia in the safety population. A frequency distribution table will be displayed by each study drug treatment period received and all subjects even though the medical history information was collected prior to dispensing study drug.

Additionally, collected data on the CRF will be listed by subject, verbatim body system, verbatim medical condition/procedure, onset date, and ongoing status/end date.

8. Study Drug Exposure and Other Medications

8.1 Study Drug Accountability

Subjects will be dispensed study drug based on fixed treatment periods at visits Day 1 (Baseline), Week 2, and Week 4. In the event the subject comes in for an unscheduled visit prior to a weekly visit, they may be dispensed additional study drug. Additional study drug may be dispensed at any study visit or unscheduled visit if the subject will need study drug beyond the two week allotment

provided at Day 1, Week 2 and Week 4. Capsule strengths for NYX-2925 are 10 mg and 100 mg. Subjects will be instructed to take 2 capsules of investigational product once daily by mouth.

The following data will be collected and derived at each start and end to the study drug accountability treatment periods/visit intervals:

Parameter	Origin/Derivation
Capsules Dispensed Amount	CRF
Capsules Returned Amount	CRF
Expected Number of Capsules Taken	Derived: Date Returned – Date Dispensed + 1 (where the maximum would be 30 because 30 capsules are issued at each dispensing visit)
Estimated Number of Capsules Taken	Derived: Number of Capsules Dispensed Amount – Number of Capsules Returned Amount
Treatment Compliance (%)	Derived: 100 x Estimated Number of Capsules Taken / Expected Number of Capsules Taken (rounded off by one number after the decimal point)

The Overall NYX-2925 Treatment Compliance (%) will be calculated as:

- 100 x ∑ (Estimated Number of Capsules Taken at All Study Drug Return Visits After NYX-2925 20 mg or 200 mg PO QD was Dispensed) / ∑ (Expected Number of Capsules Taken at All Study Drug Return Visits After NYX-2925 20 mg or 200 mg PO QD was Dispensed) and rounded off by one number after the decimal point

A subject will be classified as being compliant with study drug administration if their calculated compliance by each treatment period and overall is between 80% and 125%, inclusive. Descriptive statistics will be summarized for treatment compliance by returning analysis visits Week 2 (Placebo), Week 4 (NYX-2925 20 mg PO QD), Week 6 (NYX-2925 200 mg PO QD), and Overall (NYX-2925 20 mg and 200 mg PO QD). The following categorical ranges will be summarized in a table for those same analysis visits and overall:

- <80%, 80-125%, >125%, and Not Reported

Any study drug not returned during a subject's visit where study drug compliance is assessed will assume that all of that study drug was taken by the subject for analysis purposes. No adjustments will be made even if comments are documented on the CRF that stated lost samples were reported by the subjects. All study drug accountability comments will be provided in a subject listing. If a subject is lost to follow-up after being dispensed study drug, then the study drug returned and overall treatment compliance will be set to missing. Any unscheduled visits will be summarized within the study treatment periods based on the study drug dispensed (Placebo, NYX-2925 20 mg PO QD, or NYX-2925 200 mg PO QD).

8.2 Study Drug Exposure

The study will include the following fixed placebo period and active treatment periods with 2 dose strengths:

- Placebo PO QD for 2 weeks
- NYX-2925 20 mg PO QD for 2 weeks
- NYX-2925 200 mg PO QD for 2 weeks

Each bottle number assigned to a subject will be verified that correct study drug was given based on the each treatment period. Any incorrect study drug bottle given where the estimated number of capsules taken defined in Section 8.1 is greater than zero, will be defined as a major protocol deviation. Study drug exposure will be listed and summarized based on the treatment periods the subjects received.

The number of study days of study drug exposure will be summarized using descriptive statistics based on the date of the last dose of study drug collected on the CRF for each treatment period. If the date/time of the last dose of study drug was not fully collected for a treatment period, then the date of returning the study drug will be used instead. If a subject is lost to follow-up after being dispensed study drug and the date of the last dose of study drug was not collected, then the number of study days will be set to missing for that specific treatment period.

8.3 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD), version 03-2016 and will be classified according to the default Anatomical Therapeutic Chemical (ATC) classification system code (up to 4 levels), WHO-DD Drug Name, and Preferred Term (PT).

Due to the nature of this study, the date and time of first dose of study drug was not collected on the CRF. Therefore, the following algorithm will be used to determine prior medications:

- Earliest Possible Medication Start Date ≤ Day 1 (Baseline) Visit Date

The following algorithm will be used to determine concomitant medications:

- Latest Possible Medication Stop Date ≥ Day 1 (Baseline)Visit Date

Depending on the start and stop dates of the medication, it is possible for a medication to be classified as both prior and concomitant.

Prior and concomitant medications will be summarized by the ATC Class Level 3 category (or Level 2 if there is not an applicable Level 3 category) and PT. Subjects may have more than one medication per ATC category and PT. At each level of subject summarization, a subject will be counted once if he/she reports one or more medications at that specific level.

The prior medication frequency distribution table will be displayed by each study drug treatment period received and all subjects even though the prior medication information was collected prior to dispensing study drug. The concomitant medication frequency distribution table will be displayed by the study drug treatment period based on the earliest possible start date described in Section 5.6.3 and prior medications that are not stopped on the Day 1 (Baseline) visit.

9. Pharmacodynamic Analyses

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12.Safety Analyses

12.1 Adverse Events

Treatment-emergent adverse events (TEAEs) will be those occurring during or after administration of the first dose of study drug until 30 days after the final dose of study drug. The date and time of first dose of study drug was not collected on the CRF for all subjects. Therefore, the following algorithm will be used to determine if the adverse events are treatment-emergent without a date and time of first dose of study drug:

- Earliest Possible AE Start Date ≥ Day 1 (Baseline) Visit and Study Drug Dispensation **and**
- Latest Possible AE Start Date ≤ 30 Days After the Final Dose of Study Drug

AEs that started prior to first dosing of study drug, but become worse in severity after receiving study drug will be considered treatment-emergent. The determination of whether or not an adverse event is classified as "treatment emergent" (i.e. TEAE) is not determined by the classification of "relationship

to study drug" collected on the CRF, but rather by the temporal relationship of the adverse event to the administration of study drug.

A related study drug TEAE is defined as any TEAE with at least a possible relationship to the study drug as assessed by the investigator or that is missing the assessment of causal relationship whose relationship to the study drug could not be ruled out. Relationships of "possibly related", "probably related", or missing are collected on the CRF, then those adverse events will be considered related study drug TEAEs. If the "unrelated" or "unlikely related" are collected on the CRF, then those adverse events will be considered not related study drug TEAEs.

Severity is assigned to each adverse event collected on the CRF. Maximum severity has the following order: "life threatening", "severe", "moderate", and "mild" as possible collection options on the CRF. A missing severity will be treated as "unknown" for analysis purposes.

All adverse events will be coded and summarized by System Organ Class (SOC) and Preferred Term (PT) based on Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 coding dictionary. This data will be summarized in a frequency distribution. Subjects may have more than one TEAE record per SOC and PT. At each level of subject summarization, a subject will be counted once if he/she reports one or more TEAE record at that specific level. For tables summarized by SOC and PT, the events will be displayed in the order of descending frequency counts for all treatments by SOC and then PT within SOC.

The number of subjects with at least one of the following adverse events, percentages for each category by treatment, and the number of total events will be included in an overall treatment-emergent adverse events summary table:

- Any TEAEs
- Related TEAEs
- Maximum Severity TEAEs
- Serious TEAEs
- Related, Serious TEAEs
- TEAEs Leading to Study Discontinuation
- Related TEAEs Leading to Study Discontinuation
- TEAEs Leading to Death

Summaries including the number of subjects and percentages of the following adverse events by SOC and PT will be provided:

- Any TEAEs
- Related TEAEs
- Maximum Severity TEAEs
- Serious TEAEs
- TEAEs Leading to Study Discontinuation

Additionally, TEAEs will be summarized by descending frequency counts of PT for all treatments. All adverse event data collected will be provided in subject listings. Subset subject listings will also be provided by serious treatment-emergent adverse events and deaths; by treatment-emergent adverse events leading to study discontinuation; any adverse events that are not considered to be treatment-emergent; by serious adverse events and deaths that are not considered to be treatment-emergent; and by adverse events leading to study discontinuation that are not considered to be treatment-emergent.

12.2 Clinical Laboratory Tests

Clinical laboratory tests for hematology, serum chemistry, and urinalysis will be summarized:

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13.Other Analyses

13.1 Protocol Deviations

Protocol deviations are collected during the study in a log maintained by the investigative site. Prior to database lock, the protocol deviations will be entered into an Excel spreadsheet and reviewed for the following reasons:

- Standard study terminology deviation categories assigned
- Severity (major versus minor) assigned
- If a subject should be excluded from the PP population

After database lock it may be determined that additional protocol deviations occurred. As a result, any additional protocol deviations found after database lock will be included with previous protocol deviations. Potential protocol deviations discovered after database lock may result excluding subjects from the PP population.

A subject listing will include the treatment period, deviation category, protocol deviation, occurrence date with the corresponding study day, severity (major versus minor), and if the protocol deviation

resulted in excluding a subject from the PP population. A frequency distribution table will be created to summarize only major protocol deviations by the assigned deviation categories.

14. Interim Analyses

An interim analysis will be performed based on a pre-database lock data cut after the 11th subject has completed the trial. Selected analyses will be completed. Given that this exploratory pilot study is single-blind and Phase 2, there will be no adjustments to Type I error.

15. Planned CSR Tables, Figures, and Listings in Section 14

The following are planned summary tables, figures, and listings (TFLs). TFLs will be numbered according to the nomenclature used to support the CSR in Section 14. The final TFL numbering may be different from the SAP. No amendment will be made for changes in TFL numbering. All titles, footnotes, and headers specified in the mock TFL shells will be displayed in the produced output unless otherwise specified. Notes to programmers will not be included in the TFLs. There will be a footnote in all TFLs that includes the SAS® version number, company creating the output, program name, the date/time that the output was produced, and the dataset(s) referenced for the output. Additional footnotes may be added to help explain/support particular data values that are not displayed in the mock TFL shells. A separate mock TFL shells document will be created to support the appearances of these planned TFLs.

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14.3 Safety and Other Data Summary Tables and Listings		
14.3.1 Adverse Event Tables		
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Appendix I: Schedule of Assessments

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