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

Amendment #6

October 14, 2021

NCT04147858

INVESTIGATIONAL PRODUCT: NYX-2925
CLINICAL PROTOCOL: NYX-2925-2005

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

Amendment #6

Sponsor: Aptinyx Inc.
[redacted]

FINAL

IND# 129731

INVESTIGATOR SIGNATURE PAGE:

The signature of the Investigator below constitutes his/her approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol as specified in both the clinical and administrative sections, including all statements regarding confidentiality. This study will be conducted in compliance with the protocol and all applicable regulatory requirements, in accordance with Good Clinical Practice, including International Council for Harmonisation Guidelines, and in general conformity with the most recent version of the Declaration of Helsinki.

Principal Investigator

_____

Printed Name

_____ _____

Signature Date

SPONSOR SIGNATURE PAGE:

This protocol will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use E6 Guideline for Good Clinical Practice, and all applicable laws and regulations including, but not limited to, those related to data privacy and clinical study disclosure.

Aptinyx Inc.

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

24-Hour Emergency Medical Contact		
Medical Monitor	[redacted]	[redacted]
Serious Adverse Event Reporting Information		
[redacted]		[redacted]

1. SYNOPSIS

Name of Sponsor Company: Aptinyx Inc.	
IND#: 129731	
Name of investigational product: NYX-2925	
Name of active ingredient: ([redacted]	
Title of Study: A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of NYX-2925 in Subjects with Fibromyalgia	
Study center(s): Approximately 52 centers in the US	
Studied period (years): Estimated date first subject enrolled: November 2019 Estimated date last subject completed: December 2021 The study period was extended due to the COVID-19 Health Emergency.	**Phase of development:** 2

Objectives:

Primary objectives:

- 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.

Secondary objectives:

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

Methodology:

Study Design

This 13- to 16-week study will include a 1- to 4-week Screening Period followed by a 12-week double-blind, randomized, placebo-controlled Treatment Period.

Visit 1 and Screening Period: Week -4 to Week -1

Each subject will be asked to provide written, informed consent for this study before any required procedures are performed. This study may employ electronic informed consent. Electronic or digital signatures (compliant with 21 CFR § 11 regulations for collecting and storing digital signatures) may be captured indicating the patient's willingness to participate in the clinical trial. The use of electronic informed consent supplements the interaction between the participant and the research staff, and it

provides an opportunity for remote conduct of study activities in the setting of the COVID-19 Health Emergency. Subjects will also be required to sign an additional consent for their inclusion in a secure, proprietary research subject database maintained by Verified Clinical Trials (VCT) [Verified Clinical Trials, Garden City, NY]. The database will use partially identified subject information to review subjects' research study history within the database. Subjects who meet any of the following criteria will not be eligible for continued screening: current enrollment in another study, concurrent screening at another research site, violation of the required number of half-lives of the investigational product in the prior research study, violation of the washout period between studies, incorrect age for the NYX-2925-2005 study, or previous randomization into a clinical trial of NYX-2925. Employees, contractors, or volunteers of the study site, Contract Research Organization (CRO), or Aptinyx, or relatives of any employee, contractor, or volunteer of the study site, CRO, or Aptinyx are not eligible to participate.

There may be up to three components in the screening period for this study: 1) After providing informed consent, subjects will participate in a screening visit where medical history, concomitant medications, scales, and eligibility to participate will be assessed; 2) Subjects who meet eligibility requirements and are taking any analgesic medications for their pain related to fibromyalgia will then be required to discontinue the analgesic medication. Subjects taking no concomitant analgesic medication for their pain related to fibromyalgia at Visit 1 may directly begin Week -1 of the Screening Period. The last dose of any prohibited analgesic must be at least two (2) weeks prior to randomization. 3) During the screening visit, subjects will be provided a handheld device to record their pain scores and rescue medication use. Prior to recording their first pain score in the handheld diary, each subject will undergo training on Accurate Pain Reporting (APR®) and Placebo Response Reduction (PRR®) via an electronic learning management system, aLearn® [Analgesic Solutions, Wayland, MA].

Subjects who have been diagnosed with fibromyalgia for greater than one (1) year are eligible for Screening. Subjects must meet the 2016 American College of Rheumatology criteria for fibromyalgia and must report at least "moderate pain" over the last week, as assessed by the Patient Global Impression of Severity (PGI-S) at the screening visit. Additional procedures during Visit 1 will include the administration of the [redacted] the Mini-International Neuropsychiatric Interview (MINI [MINI version 7.0.2 for DSM-5™]), completion of the Sheehan Suicidality Tracking Scale (S-STS), serious adverse event collection (will be collected from the time informed consent is obtained through 30 days after the last dose of study drug),) demographic characteristics, medical history including prior and concomitant medications, complete physical examination (with comprehensive neurological examination), tripilicate electrocardiograms (ECGs [three separate ECGs] with a minimum of a two minute interval), vital signs (blood pressure and pulse after sitting or lying supine for at least five minutes), height, body weight, and collection of blood (8 hour fast) samples for chemistry, hematology, human immunodeficiency virus and hepatitis testing, and urine samples for urinalysis. Vital signs may be repeated up to three times at screening, per the Investigator's discretion. All vital signs should be recorded in the subject's source documents, with the final measurement of vital signs being entered into the eCRF system. All subjects will undergo a drug screen using a local urine testing kit. Subjects who test positive for benzodiazepines or opioids inconsistent with current prescriptions, psychoactive cannabinoids (e.g., marijuana, THC) inconsistent with subject reported use, PCP, cocaine, or amphetamines will not be allowed to continue in the study. Female subjects of childbearing potential will be tested for pregnancy using a local urine testing kit and will be counseled to begin or continue using highly effective contraception.

Eligible subjects who meet all entry criteria will enter a 1- to 4-week Screening Period, during which they will discontinue all their analgesic treatments for pain related to fibromyalgia, and complete daily pain diaries. The duration of the Screening Period will depend upon the analgesic treatment that is being discontinued (see Section 15.1 of the protocol for Disallowed Analgesic and Other Medications). The discontinuation of analgesic medication(s) will be managed by the Principal Investigator or designee at

the investigative site, as applicable. Subjects taking no analgesic medication at Visit 1 may directly begin Week -1 of the Screening Period.

During Visit 1, eligible subjects will be provided a handheld device and, as a method for ensuring consistency and reliability of pain scoring, subjects will be instructed at all study visits on how to record their pain scores and rescue medication use on the device. Subjects will also be educated at screening on Accurate Pain Reporting® and Placebo Response Reduction® (APR® and PRR® training [Analgesic Solutions, Wayland, MA]) and provided refresher training at all site-based study visits, via the aLearn® learning management system portal (Analgesic Solutions, Wayland, MA). This training is mandatory prior to randomization and at each site-based visit throughout the study, with the exception of the final visit. Subjects will be reminded at all visits of appropriate expectations for their participation in a clinical study and the importance of consistently and accurately reporting their pain throughout the study.

Subjects will be dispensed acetaminophen to be used as rescue medication (RM) and will be instructed to take one to two 500 mg tablets every 6 hours as needed for pain related to fibromyalgia, not to exceed three (3) grams of acetaminophen per day.

For pain unrelated to fibromyalgia, subjects may use a nonsteroidal anti-inflammatory drug (NSAID) for up to two (2) days during a seven (7) day period. If the need for analgesics exceeds this period, the patient should call the Investigator to evaluate the cause of pain and the course of action. If a subject requires a NSAID for pain unrelated to fibromyalgia, the medication should be recorded as a concomitant medication and the adverse event must be recorded in the eCRF.

Beginning at Week-1, fibromyalgia related pain intensity and rescue medication use will be recorded in the study-issued handheld device daily at bedtime. Subjects will enter their average pain intensity and total rescue medication use during the past 24 hours. Pain intensity will be recorded using an 11-point NRS, with 0 being no pain and 10 being the worst possible pain. Every morning upon awakening, subjects will complete the Daily Sleep Interference Scale (DSIS) via their study-issued handheld device.

The following scales will be completed at the Screening Visit (Visit 1): PGI-S, 2016 ACR Fibromyalgia Criteria, [redacted] MINI, and the S-STS.

Screening Period: Week -1(as needed)

Subjects taking no concomitant analgesic medication for their fibromyalgia at Visit 1 may directly begin Week -1 of the Screening Period.

Baseline Visit: Week 0/Visit 2

At Visit 2 (Baseline Visit), study personnel will verify eligibility with the inclusion and exclusion criteria while the subjects are on site and perform safety assessments.

The appropriate use of rescue medication will be assessed by inventory of the returned tablets, as well as by subject interview. Use of concomitant medications will be documented. Additional procedures during Visit 1 will include the S-STS, an electrocardiogram and vital signs (blood pressure and pulse after sitting or lying supine for at least five minutes). Blood (8 hour fast) and urine samples will be collected for hematology, chemistry, and urinalysis testing. Subjects will undergo a drug screen using a local urine testing kit. Subjects who test positive for benzodiazepines inconsistent with protocol specified allowed prescriptions, psychoactive cannabinoids (e.g., marijuana, THC) inconsistent with subject reported use, opioids, PCP, cocaine, or amphetamines will not be allowed to continue in the study. Female subjects of childbearing potential will be tested for pregnancy using a local urine testing kit and will be counseled to continue using highly effective contraception.

Pain scores reported by subjects during the Screening Period will be evaluated by the interactive response technology (IRT) system for raw score and for variability among scores after transmission of

pain scores from the handheld devices to determine randomization eligibility. Subjects whose mean of the daily average pain intensity score during the preceding seven (7) days is within the protocol-defined algorithm and whose compliance with daily diary completion is 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 will notify the site if the subject is "Eligible" or "Not eligible." No other information will be provided.

Eligible subjects will be randomized to receive either oral NYX-2925 50 mg, NYX-2925 100 mg or placebo daily for 12 weeks. Investigators and subjects will be both blinded to treatment allocation and masked to the randomization criteria.

Subjects will be dispensed a four-week supply of study drug and instructed to take one (1) capsule by mouth once daily. The first dose of study drug will be taken in the clinic during Visit 2 (Week 0). Subjects will be instructed to take study medication one time per day throughout the study. Acetaminophen will be dispensed/re-dispensed for use as rescue medication for pain related to fibromyalgia; instructions to take no more than 3 g/day (one to two 500 mg tablets every 6 hours as needed) will be reinforced.

Adverse event collection will begin from the time of study drug administration through the last day of the subject's participation in the study.

Subjects will be instructed to continue entering their average pain intensity and rescue medication use over the past 24 hours into their study issued handheld device every night. Every morning upon awakening, subjects will complete the DSIS and confirm they have taken their study medication for the day via their study-issued handheld device. Diary compliance will be reviewed at each study visit by the study staff, and reporting instructions will be reinforced. Subjects will be reminded on appropriate expectations around their participation in a clinical study and the importance of consistently and accurately reporting their pain intensity throughout the study. Review of the APR® and PRR® materials will be repeated for all subjects as refresher training or based on findings of an ongoing blinded data review (e.g., if pain score variability is increased on a subject or site level) via the aLearn® portal.

The following scales will be completed at the Baseline Visit (Visit 2): the Fibromyalgia Impact Questionnaire - Revised (FIQR), [redacted] the Patient Reported Outcomes Measurement Information System – Fibromyalgia ($PROMIS_{FM}$) [Sleep Disturbance Short Form, Fatigue Profile Short Form, Physical Function Short Form], PGI-S and S-STS.

The subject will be given a printed copy of the study specific S-STS to take home and complete during the Week 2/Visit 3 telephone or videoconference visit.

Treatment Period: Week 2/Visit 3

Subjects will be contacted by the clinic via telephone or videoconference at the end of Week 2 (Visit 3) for assessment of compliance with study drug, use of rescue medication and diary entries. The appropriate use of study drug and rescue medication will be assessed by subject interview. Subjects will be reminded to take one capsule of study drug by mouth once daily. The subject will be reminded not to exceed 3 g/day (one to two 500 mg tablets every 6 hours as needed) of rescue medication for pain related to fibromyalgia.

Diary compliance will be reviewed by the study staff and reporting instructions will be reinforced. Adverse events will be assessed by asking the subjects a nonleading question. Misuse and abuse-related events will be assessed using the Misuse, Abuse, and Diversion Drug Event Reporting System® (MADDERS [Analgesic Solutions, Wayland, MA]). Use of concomitant medications will be documented.

Subjects will be instructed to continue entering their average pain intensity and rescue medication use over the past 24 hours into their study-issued handheld device every night. Every morning upon awakening, subjects will complete the DSIS and confirm they have taken their study medication for the day via their study-issued handheld device. Subjects will be reminded on appropriate expectations around their participation in a clinical study and the importance of consistently and accurately reporting their pain throughout the study. Review of these educational materials may be repeated for some subjects at this remote visit as refresher training or based on findings of an ongoing blinded data review (e.g., if pain score variability is increased on a subject or site level) via the aLearn® portal, at the Investigator's discretion.

The subject will be asked to complete the printed copy of the S-STS given to them at their Baseline Visit while communicating with the site staff. The staff will review the subject's answers to the S-STS and recommend corrections, only where the form has been completed incorrectly. The completed S-STS source document will be mailed back to the clinic or returned at the next study visit to be filed in the subject's chart and the data entered into the eCRF system.

A subject may be asked to return to the clinic, per Investigator discretion, for additional study specific training or examination. Any unscheduled return to the clinic visit should be entered as an Unscheduled Visit in the eCRF and IRT systems.

The following scale will be completed at Week 2 (Visit 3): S-STS

Treatment Period: Week 4/Visit 4 and Week 8/Visit 5

Subjects will return to the clinic at the end of study Week 4 (Visit 4), and Week 8 (Visit 5) for assessment of compliance with study drug and use of rescue medication. The appropriate use of study drug and rescue medication will be assessed by inventory of the returned study drug and rescue medication, as well as by subject interview. Subjects will be dispensed a four-week supply of study drug. Subjects will be instructed to take one capsule of study medication by mouth once dailyThe rescue medication will be dispensed/re-dispensed with instructions not to exceed 3 g/day (one to two 500 mg tablets every 6 hours as needed) of acetaminophen for fibromyalgia related pain.

Pain diary compliance will be reviewed by the study staff and reporting instructions will be reinforced.

Adverse events will again be assessed by asking the subjects a nonleading question. Misuse and abuse-related events will be assessed using MADDERS (Analgesic Solutions, Wayland MA). Use of concomitant medications will be documented. Vital signs (blood pressure and pulse after sitting or lying supine for at least five minutes) will be measured. Blood (8 hour fast) and urine samples will be collected for chemistry, hematology, and urinalysis testing. Subjects will undergo a drug screen using a local urine testing kit. Female subjects will be tested for pregnancy using a local urine testing kit, if clinically indicated for females of childbearing potential. Female subjects of childbearing potential will be counseled to continue using highly effective contraception.

Subjects will be instructed to continue entering their average pain intensity and rescue medication use over the past 24 hours into their study-issued handheld device every night. Every morning upon awakening, subjects will complete the DSIS and confirm they have taken their study drug for the day via their study-issued handheld device, once completed. Subjects will be reminded on appropriate expectations around their participation in a clinical study and the importance of consistently and accurately reporting their pain throughout the study. Review of these educational materials will be repeated for all subjects at each site-based study visit via the aLearn® portal., with the exception of the final visit.

The following scales will be completed at Week 4 (Visit 4), Week 8 (Visit 5): FIQR, [redacted] $PROMIS_{FM}$, Patient Global Impression of Change (PGI-C) and S-STS.

Treatment Period: Week 12/Visit 6 or Early Termination Visit

During Week 12 (Visit 6) or the Early Termination Visit, subjects will return to the clinic for assessment of compliance with study drug and rescue medication use. The appropriate use of study drug and rescue medication will be assessed by inventory of the returned study drug and rescue medication, as well as by subject interview. Subjects will return the study-issued handheld device and any other study related materials to the study site.

Pain diary compliance will be reviewed by the study staff. Adverse events will be assessed by asking the subjects a non-leading question. Misuse and abuse-related events will be assessed using MADDERS (Analgesic Solutions, Wayland, MA).

Use of concomitant medications will be documented. Vital signs (blood pressure and pulse after sitting or lying supine for at least five minutes) and body weight will be measured, a brief physical examination will be performed and subjects will undergo an electrocardiogram. Blood (8 hour fast) and urine samples will be collected for chemistry, hematology, and urinalysis testing. Female subjects of childbearing potential will be tested for pregnancy using a local urine testing kit. Subjects will undergo a drug screen using a local urine testing kit.

The site will contact the subjects by telephone within 7-10 days to complete a safety follow-up call. The Investigator, at their discretion, may ask subject to return for an Unscheduled Visit for any safety concerns, abnormal laboratory or ECG findings. A final call will be made to the subject approximately 30 days after the final visit to assess for AE closure and any new SAEs.

The following scales will be completed at Week 12 (Visit 6)/Early Termination Visit: FIQR, [redacted] $PROMIS_{FM}$, PGI-C, and S-STS.

Number of subjects (planned and analyzed):

Approximately 300 subjects will be randomized.

Inclusion Criteria: Screening

Subjects must meet ALL the following criteria to be enrolled in this study:

1. An Institutional Review Board approved written informed consent and privacy language (Health Insurance Portability and Accountability Act (HIPAA)) authorization must be obtained from the subject prior to performing any study-related procedures.
2. Subject provides separate consent to being included in a research subject database.
3. Subject is ≥18 and ≤75 years of age.
4. Subject must meet the following 3 conditions described in the 2016 American College of Rheumatology criteria for fibromyalgia [Wolfe 2016]:
    a) Widespread Pain Index ≥7 and Symptom Severity Score ≥5, or the Widespread Pain Index is 4 to 6 and the Symptom Severity Score is ≥9.
    b) Symptoms have been present at a similar level for ≥3 months; and
    c) Pain is generalized and present in at least 4 of 5 regions.
5. Subject has a history of fibromyalgia that was diagnosed >1 year prior to Screening.
6. Subject reports at least moderate pain over the last week, as assessed by PGI-S at Visit 1.
7. Subject agrees to use only acetaminophen treatment as needed for breakthrough pain related to fibromyalgia.

8. Subject agrees not to initiate or change any non-pharmacologic interventions (including normal daily exercise routines, chiropractic care, physical therapy, psychotherapy, and massage therapy) during the study. Any ongoing non-pharmacologic intervention must be stable for at least 30 days prior to screening.
9. Subject has a body mass index (BMI) ≤40 kg/m^2.
10. Subject's calculated creatinine clearance is ≥60 mL/minute (Cockcroft-Gault formula).
11. Absence of impaired hepatic function characterized by a previous known diagnosis of chronic liver disease, and/or the presence of abnormal serum total bilirubin (TBL), or alanine transaminase (ALT), aspartate transaminase (AST), or alkaline phosphatase (ALP) >1.5x upper limit of normal (ULN) at screening.
12. Except as noted in criteria 10 and 11, subject's clinical laboratory values are within normal limits or deemed not clinically significant by the Investigator.
13. Female subjects of child bearing potential with a negative pregnancy test prior to entry into the study and who are practicing a highly effective method of birth control (e.g., oral or parenteral contraceptives, intrauterine device, barrier [condom and spermicide], abstinence) and who do not plan to become pregnant, breastfeed, or donate ova during the course of the study and for 28 days after the final administration of investigational product.
14. Male subjects should use a highly effective method of birth control and refrain from sexual activity with female sexual partners who do not use a highly effective method of birth control during the study. Male subjects who are not surgically sterilized for at least 90 days prior to screening and sexually active with female partner(s), must agree to use barrier contraception (condom with spermicide) during the study. Subjects must agree to refrain from sperm donation during the study and for 90 days after the final administration of investigational product.
15. Subject has not participated in an interventional study for at least 30 days or has not taken investigational study medication for a period of at least 5 half-lives of the study medication, whichever is longer. Agrees not to participate in another interventional study while on treatment. Eligibility will be reviewed during the study via sponsor participation in a research subject database.
16. Subject has the ability to understand the requirements of the study, abide by the study restrictions, as well as concomitant medications exclusions and agrees to return for the required assessments.

Exclusion Criteria:

Subjects who meets ANY of the following criteria will be excluded from the study:

1. Lifetime history of any psychotic and/or bipolar disorder.
2. Subjects with uncontrolled major depressive disorder or generalized anxiety disorder, in the investigator's opinion (subjects may have been on a stable protocol allowed medication for greater than 60 days prior to screening), or are not expected to remain stable for the duration of the study.
3. Pain due to diabetic peripheral neuropathy, post-herpetic neuralgia, traumatic injury, prior surgery, complex regional pain syndrome, or other source of pain that, in the investigator's opinion, would confound or interfere with the assessment of the subject's fibromyalgia pain or require excluded therapies during the subject's study participation.

4. Pain due to concurrent autoimmune, infectious, or inflammatory disease such as rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease, or other chronic widespread pain condition(s) that may confound fibromyalgia pain reporting.
5. Any impairment, activity or situation that, in the judgment of the Investigator, would prevent satisfactory completion of the study protocol.
6. An untreated endocrine disorder that may confound fibromyalgia assessments.
7. History of severe renal impairment defined by currently receiving hemodialysis or peritoneal dialysis,or has undergone a previous renal transplant.
8. Known history of significant cardiovascular condition, such as myocardial infarction within the past year, or moderate to severe congestive heart failure (New York Heart Association [NYHA] Class III and IV); evidence of current uncontrolled cardiac arrhythmias, angina; electrocardiographic evidence of acute ischemia or clinically significant conduction system anomalies; QTcF >450 msec (males) or >470 msec (females); or uncontrolled hypertension characterized by resting systolic blood pressure >160 mm Hg or resting diastolic >100 mm Hg, or clinically significant hypotension in the judgement of the Investigator as characterized by resting systolic blood pressure <90 mm Hg or resting diastolic blood pressure <60 mm Hg accompanied by symptoms such as lightheadedness, dizziness, and profound fatigue or signs such as irregular heartbeat.
9. Resting heart rate <45 bpm or >95 bpm.
10. History of Huntington's disease, Parkinson's disease, Alzheimer's disease, multiple sclerosis, or a history of seizures (with the exception of childhood febrile seizures), epilepsy, or stroke.
11. Subject has evidence of any clinically significant, uncontrolled gastrointestinal, endocrinologic , hematologic, immunologic, metabolic, urologic, pulmonary (including uncontrolled, obstructive sleep apnea), neurologic, dermatologic, and/or other major disease (exclusive of fibromyalgia) that may interfere with study participation, as assessed the investigator.
12. Positive serology test for human immunodeficiency virus (HIV) or current hepatitis B or C hepatitis infection, or other ongoing infectious disease that the investigator considers clinically significant.
13. Concomitant use of protocol specified prohibited medications from which subject is unable to wash-out (see Section 8.7 of the protocol for Concomitant Medications Restrictions).
    a. Washout from excluded medication allowed only if the Investigator deems it medically appropriate.
    b. Washout should be completed during screening, with the last dose being at least two (2) weeks prior to randomization (See Section 15.1 of the protocol for Disallowed Analgesic and Other Medications).
14. Sensitivity or allergy to N-methyl-D-aspartate receptor ligands including ketamine, esketamine, memantine, as well as amantadine, dextromethorphan, methadone, dextropropoxyphene, and/or ketobemidone.
15. Use of NMDAR-binding drugs (e.g., ketamine, esketamine, memantine) as well as amantadine, dextromethorphan, methadone, dextropropoxyphene, and/or ketobemidone) within 30 days prior to dosing or during the study.
16. Sensitivity to or intolerance to acetaminophen or associated formulation components.

17. Current or recent (within 12 months of screening) history of a substance use disorder including cannabinoid and/or alcohol use disorder as determined using the standard MINI version 7.0.2 for DSM-5™.
18. a. Positive urine drug screen for benzodiazepines or opioids inconsistent with current prescriptions, psychoactive cannabinoids (e.g., marijuana, THC) inconsistent with subject reported use, PCP, cocaine, or amphetamines Visit 1.

    b. Positive urine drug screen for benzodiazepines inconsistent with protocol specified allowed prescription, psychoactive cannabinoids (e.g., marijuana, THC) inconsistent with subject reported use, opioids, PCP, cocaine, or amphetamines at Visit 2.
19. Hypersensitivity or intolerance to multiple medications, in the opinion of the Investigator.
20. Meets the criteria for suicidal intent, plan and/ or behavior by scoring 3 or 4 on Questions 2 or 13, or 2 or higher on any Question 1a (only if 1b is coded YES), 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 14 based on the S-STS, or who is at significant risk to commit suicide, as assessed by the investigator, at Visit 1 or Visit 2.
21. Planned surgery during study participation.
22. Active malignancy or a history of malignancy (except for treated non-melanoma in-situ skin cancer) within 5 years of screening.
23. Subject has filed for a disability claim or has any pending worker's compensation litigation.
24. Employee, contractor, or volunteer of the study site, CRO, or Aptinyx, or relative of any employee, contractor, or volunteer of the study site, CRO, or Aptinyx or previous randomization into any clinical trial for NYX-2925.
25. Any condition, including serious medical conditions, that could interfere with the ability of the subject to participate in the study or could confound study assessments.
26. History of severe infection with COVID-19 requiring hospitalization, treatment with oxygen or mechanical ventilation, that may interfere with study participation, as assessed the investigator.
27. Any subject with a medical history of COVID-19 infection (positive test) within the last two (2) months, or current symptoms consistent with COVID-19 infection (not tested), e.g. loss of smell, sore throat, cough or fever (2 or more symptoms at the same time), as assessed by the investigator.

Inclusion Criteria: Randomization

Daily pain scores and diary compliance will be transferred into the interactive response technology system, which will be used to assess the criteria for randomization. Subjects whose mean of the daily average pain intensity score during the preceding seven (7) days is within the protocol-defined algorithm and with adequate compliance with daily diary completion will be eligible for randomization.

Waivers to the inclusion or exclusion criteria will NOT be allowed.

Test products doses and mode of administration:

NYX-2925 50 mg oral capsules, one capsule once daily by mouth

NYX-2925 100 mg oral capsules, one capsule once daily by mouth

Reference therapy, dose and mode of administration:

Placebo, oral capsules, one capsule once daily by mouth

Rescue medication:

Acetaminophen, up to 3 g/day, as needed for pain related to fibromyalgia. To be dispensed beginning at Visit 1 and re-dispensed and/or replenished throughout the entire study.

Duration of Study

Screening: One (1) to four (4) weeks. Prohibited analgesic medications for fibromyalgia need to be discontinued with the last dose taken at least two (2) weeks prior to randomization.

Maintenance: Twelve weeks of blinded treatment with either NYX-2925 50 mg QD, NYX-2925 100 mg QD or placebo QD.

Criteria for Evaluation:

Efficacy:

Primary Efficacy Endpoint:

- Change from baseline in the weekly mean of the daily Numerical Rating Scale (NRS) score assessing average pain intensity in the past 24 hours

Secondary Efficacy Endpoints

- 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 subjects achieving ≥30% 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 Outcomes Measurement Information System – Fibromyalgia ($PROMIS_{FM}$) sleep disturbance score
- Change from baseline to Week 12 in the Patient Reported Outcomes Measurement Information System – Fibromyalgia ($PROMIS_{FM}$) fatigue profile score
- Change from baseline to Week 12 in the Patient Reported Outcomes Measurement Information System – Fibromyalgia ($PROMIS_{FM}$) 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

Other Efficacy Endpoints:

Safety Endpoints:

- Adverse events and serious adverse events
- Discontinuations due to adverse events
- S-STS

Sample Size:

The planned sample size is 300 randomized subjects. This will provide approximately 80% power for statistical testing with an overall Type I error rate of 0.05.

Statistical methods:

Safety analyses will be based on the Safety Population, defined as all subjects who receive at least one (1) dose of study drug. Efficacy analyses will be based on the modified Intent-to-Treat Population, defined as all subjects in the Safety Population with at least one (1) postbaseline assessment of the weekly mean of pain intensity NRS.

Change from baseline will be assessed for treatment group differences with a mixed model repeated measures (MMRM) with factors for study site, treatment, week, and the treatment-by-week interaction, with baseline value as a covariate.

As a sensitivity analysis, an analysis of covariance (ANCOVA) with fixed factors for study site and treatment, with baseline value as a covariate will be used.

Change in the weekly mean of the daily NRS scores assessing average pain intensity in the past 24 hours from baseline will be assessed for treatment group differences using an MMRM and ANCOVA analogous to the primary efficacy analysis described above. Change from baseline for the FIQR, [redacted] DSIS and $PROMIS_{FM}$ (sleep disturbance, fatigue profile and physical function) will be analyzed similarly. The PGI-C will be summarized at each evaluation.

The use of rescue medication will be summarized descriptively. The percentage of subjects achieving ≥30% reduction in the mean NRS average pain intensity, the percentage of subjects achieving ≥50% reduction in the mean NRS average pain intensity and sustainability of pain reduction in the mean NRS average pain intensity will be summarized.

The number of days to the first ≥30% reduction and number of days to first ≥50% reduction in the mean NRS average pain intensity will be assessed for treatment group differences with the log-rank test.

Adverse events will be categorized by system organ class and preferred term with the Medical Dictionary for Regulatory Activities (MedDRA). Summary tables for treatment-emergent adverse events (TEAEs) will include number and percent of subjects experiencing TEAEs by system organ class and preferred term.

Mean change in clinical laboratory and vital signs from baseline will be summarized descriptively. Clinical laboratory results considered clinically important by the Investigator will be identified.

Subjects with suicidal ideation or behavior will be identified with the S-STS.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and special terms are used in this study protocol.

Table 2: Abbreviations and Special Terms

Abbreviation	Explanation
ACR	American College of Rheumatology
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
ANCOVA	analysis of covariance
APR®	Accurate Pain Reporting®
AST	aspartate transaminase
BOLD	whole-brain blood oxygenation level dependent
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
CRP	C-reactive protein
CSF	cerebrospinal fluid
DSIS	Daily Sleep Interference Scale
DSM-5™	Diagnostic and Statistical Maunal of Mental Disorders – Fifth Edition
ECG(s)	Electrocardiogram(s)
eCRF	electronic case report form
fcMRI	functional connectivity magnetic resonance imaging
FDA	Food and Drug Administration
FIQR	Fibromyalgia Impact Questionnaire - Revised
Free T_4	free thyroxine
GAD	generalized anxiety disorder
GCP	Good Clinical Practice
GLx	glutamate + glutamine metabolites
[redacted]	[redacted]
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HMRS	proton magnetic resonance spectroscopy
ICA	independent component analysis
ICF	informed consent form

Abbreviation	Explanation
ICH	International Council for Harmonisation
IRB	Institutional Review Board
IRT	interactive response technology
MADDERS	Misuse, Abuse, and Diversion Drug Event Reporting System®
MDD	major depressive disorder
MDE	major depressive episode
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini-International Neuropsychiatric Interview
MMRM	mixed model for repeated measures
NF	National Formulary
NMDA	*N*-methyl- D -aspartate
NMDAR	*N*-methyl-D-aspartate receptor
NRS	numeric rating scale
NSAID(s)	nonsteroidal anti-inflammatory drug(s)
NYHA	New York Heart Association
pDPN	painful diabetic peripheral neuropathy
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
$PROMIS_{FM}$	Patient Reported Outcomes Measurement Information System – Fibromyalgia
PRR®	Placebo Response Reduction®
REM	rapid eye movement
RM	rescue medication
SAE	serious adverse event
S-STS	Sheehan Suicidality Tracking Scale
T_3	Triiodothyronine
T_4	Thyroxine
TBL	total bilirubin
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
TSH	thyroid stimulating hormone
VCT	Verified Clinical Trials
ULN	upper limit of normal

Abbreviation	Explanation
USP	United States Pharmacopeia

Note: Abbreviations that appear only in tables or figures are defined in the appropriate tables or figures.

4. INTRODUCTION

NYX-2925 is a novel small molecule being developed for the treatment of neuropathic pain and fibromyalgia. This molecule interacts with N-methyl-D-aspartate receptors (NMDARs) through a novel binding domain and acts as a co-agonist with glutamate. NYX-2925 appears to act at a binding site that is distinct from NMDAR agonists or antagonists studied to date, such as D-cycloserine, ketamine, MK-801, or kynurenic acid. The NYX-2925 mode of action is distinct from that of all existing and emerging drugs that are indicated for the treatment of neuropathic pain and fibromyalgia. While current medications target individual elements of pain signal transmission or modulation, NYX-2925 modulates multiple synaptic relays within pain circuits.

Glutamate is the major excitatory neurotransmitter in the central nervous system and acts through activation of glutamate receptors. A portion of the receptors bind preferentially to *N*-methyl-D-aspartate (NMDA), and are, therefore, termed NMDARs. Unlike other glutamate receptors found in the brain, such as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid or kainic acid receptors, the NMDARs are unique in that they have distinct binding sites for both glutamate and glycine, and binding by both ligands is required for receptor activation. The NMDARs are implicated in a number of physiological and pathological processes, including anxiety, cognition, learning, stroke, schizophrenia, Parkinson's disease, and neuropathic pain [Tai 2001; Mony 2009; Traynelis 2010].

Fibromyalgia is a chronic, debilitating, disorder typified by widespread musculoskeletal pain, accompanied by symptoms of fatigue, affected sleep, memory issues, and mood disorders. It is estimated that fibromyalgia affects 5 million people or 2 to 5% of the American adult population [Arnold 2012]. Women are more commonly diagnosed than men (female:male ratio is 7:1) and prevalence increases with age.

Individuals suffering from fibromyalgia presently have limited treatment options available. Current treatment options include pregabalin, a calcium channel alpha-2-delta subunit ligand, and two norepinephrine and serotonin reuptake inhibitors, duloxetine and milnacipran. These therapies have shown some efficacy in treating fibromyalgia symptoms, although for a large proportion of patients, treatment is insufficient.

Recent research suggests that the chronic widespread pain seen in fibromyalgia patients has a neurogenic origin. Higher levels of ascending pathway neurochemicals, including nerve growth factor, substance P, and brain-derived neurotrophic factor, are present in the cerebrospinal fluid (CSF) of fibromyalgia patients when compared to healthy controls. In addition, glutamate levels can be elevated in both the CSF and brain of fibromyalgia patients. Glutamate may play a central role by acting on NMDARs to increase the central amplification of pain perception, which is thought to manifest as allodynia and hyperalgesia in fibromyalgia patients [Clauw 2011]. NMDA receptors are thus an attractive target for fibromyalgia therapeutic drug development.

As in fibromyalgia, the central nervous system modulates the experience of pain in people with neuropathic pain, with the rostroventral medial medulla [Silva 2016], the dorsal anterior cingulate cortex [Russo 2015], the insula, and other brain regions [Ossipov 2010] all thought to be involved. Neuropathic pain is caused by disease or injury of the somatosensory system as opposed to nociceptive pain, where the sensory system is physiologically normal [Jensen 2014]. While neuropathic pain can initially arise within the central or the peripheral nervous system

through a wide range of etiologies, central nervous system modulation of the experience of pain is common, regardless of the specific precipitating factors or initial location of the pain.

Preclinical pharmacology studies support the study of NYX-2925 in both fibromyalgia and neuropathic pain, both of which are chronic pain syndromes involving central nervous system modulation of pain signals. NYX-2925 is effective in several models of neuropathic pain and has shown activity in the chronic unpredictable stress model of fibromyalgia. Animal models of neuropathic pain in which NYX-2925 was tested include the rat Bennett model of neuropathic pain, the rat streptozotocin model of diabetic peripheral neuropathy, and the rat Taxol® model of chemotherapy-induced neuropathic pain. Unlike gabapentin (150 mg/kg orally), NYX-2925 (1 to 30 mg/kg orally) produced a rapid and long-lasting analgesia in the rat Bennett model of neuropathic pain without changes in locomotor activity after a single dose. Further, in the chronic unpredictable stress model of fibromyalgia, NYX-2925 (10 mg/kg) has been shown to produce mechanical analgesia. In summary, these data support testing NYX-2925 in both fibromyalgia and neuropathic pain.

Pharmacokinetic studies in rats and dogs suggest that NYX-2925 is rapidly absorbed into the bloodstream, with time to peak plasma concentration being reached within one hour. NYX-2925 is rapidly eliminated from plasma, with an apparent terminal elimination half-life in the range of four to five hours in rats and one to two hours in dogs. Brain exposure is approximately 5% to 10% relative to plasma levels of NYX-2925 in rats.

Both single-dose and daily repeat-dose toxicology studies have been performed in rats and dogs. The maximum tolerated dose following a single oral exposure is at least 1000 mg/kg in both rats and dogs. After up to 13 weeks of daily oral administration in rats and dogs, the no-observed- -effect level (NOEL) was the highest dose tested for rats (1000 mg/kg/day) and the no-observed-adverse-effect level (NOAEL) was 120 mg/kg/day in dogs. There were no adverse findings in rats. In a 42-day, repeat-dose dog study, minimal or mild changes were observed in liver parameters at the high dose of 180 mg/kg/day. Similar changes were observed in the 13-week, repeat-dose dog study at the high dose of 240 mg/kg/day: liver enzyme levels in plasma were increased, and microscopic examination of the liver revealed pigmented material within bile canaliculi and in the cytoplasm of hepatocytes. These changes in liver parameters were partially reversed after a two-week or four-week recovery phase. In the 13-week repeat-dose study in dog, these observations were considered adverse at 240 mg/kg/day; therefore, the NOAEL was 120 mg/kg in dog. Based on the data to date, the plasma levels (exposure) of NYX-2925 at the NOAEL of 120 mg/kg/day in dog, the most sensitive species, is considered to be approximately 70 and 20-fold the human dose of 50 mg and 150 mg, respectively.

As of June 2019, the clinical development program for NYX-2925 includes two completed Phase 1 studies in healthy volunteers, one ongoing, clinically complete Phase 1 study in healthy volunteers, one ongoing, clinically complete Phase 2 study in subjects with diabetic peripheral neuropathy (DPN), and one ongoing, clinically complete Phase 2 study in subjects with fibromyalgia. NYX-2925 exposure includes 154 healthy volunteers, 301 subjects with DPN, and 23 subjects with fibromyalgia.

In NYX-2925-1001, a Phase 1 single and multiple ascending dose safety and tolerability study in healthy volunteers, pharmacokinetic analysis revealed that absorption of NYX-2925 was relatively rapid; peak concentrations were achieved within two hours after dosing and declined in a roughly monophasic manner over 24 hours. The pharmacokinetic profiles were dose-

proportional over the dose range tested and showed minimal accumulation following once daily dosing for seven days. A high-fat, high-caloric meal decreased the rate of absorption and lowered peak plasma concentration by 10%, but had no impact on the extent of exposure, suggesting that the compound may be administered with or without food. The majority (approximately 60% to 70%) of the administered dose was eliminated as unchanged NYX-2925 in the urine. Central nervous system exposure was confirmed, and CSF concentrations increased proportionally as the dose increased.

NYX-2925-1003 was a Phase 1 randomized, double-blind, placebo-controlled, crossover study of the effects of NYX-2925 on sleep architecture in healthy male volunteers. Preliminary PD results from this study indicate that a single oral dose of 100 mg NYX-2925 in healthy subjects increased sleep efficiency (total sleep time) as well as non-rapid eye movement (NREM) sleep time without affecting rapid eye movement (REM) sleep or inducing daytime drowsiness in the placebo/NYX-2925 arm.

NYX-2925-1004 was a Phase 1 double-blind, randomized, sponsor-open, parallel, placebo-controlled exploratory study to assess the effect of multiple dose levels (10, 50, or 200 mg) of NYX-2925 on the brain function of healthy volunteers as measured by EEG and event-related potentials (ERPs). NYX 2925 was shown to acutely enhance NMDAR-dependent mismatch negativity (MMN) at the lowest dose tested (10 mg single dose) and quantitative electroencephalogram (EEG) changes along with auditory long-term plasticity changes were seen across the dose levels. This study also showed auditory long-term plasticity changes 3 and 7 days after a single dose.

In Phase 2 Study NYX-2925-2001, 301 subjects with neuropathic pain associated with DPN were evaluated for change in pain scores over the four-week treatment period comparing placebo to NYX-2925 (10, 50, or 200 mg). Overall, there were no significant differences between NYX- 2925 and placebo with regard to the changes in pain scores over the four-week treatment period. A numerical improvement in change in average pain intensity compared with placebo was observed for NYX-2925 50 mg and 200 mg, especially in subjects not taking any concomitant analgesic medication. Sleep interference due to pain showed a trend toward improvement for NYX-2925 50 mg. A significant ($p < 0.01$) improvement from baseline in average daily pain intensity at Weeks 3 and 4 was observed for NYX-2925 50 mg compared to placebo in the post hoc analysis of subjects with ≥ 4 years of DPN.

A Phase 2 Study, NYX-2925-2002, was conducted in 22 women with a confirmed diagnosis of fibromyalgia. In a sequential manner, all subjects were to receive daily doses of placebo, 20 mg NYX-2925 and 200 mg NYX-2925 for two weeks each. At baseline and during each two-week treatment period, subjects underwent a series of functional magnetic resonance imaging (*f*MRI) scans, combined with proton magnetic resonance spectroscopy (^{1}H-MRS) to measure key brain activity markers known to be associated with central pain perception and processing. These were the primary outcome measures for this trial. Secondary endpoints included patient reported outcomes of average daily pain and worst daily pain measured using a numberic rating scale (NRS), the impact of fibromyalgia on the subjects' daily living measured by the revised Fibromyalgia Impact Quesionnaire (FIQR) and Patient Reported Outcomes Measurement Information System – Fibromyalgia ($PROMIS_{FM}$). At Week 6, under the 200 mg treatment condition, preliminary analysis of the data suggest there were significant improvements with NYX-2925 compared to placebo using the above measures. Pharmacodynamic results from this

study revealed that NYX-2925 20 mg significantly reduced glutamate + glutamine (Glx) levels within the posterior insula, a region previously implicated in pain processing in fibromyalgia. Based on preliminary analyses, significant clinical improvements in exploratory endpoints were observed following treatment with NYX-2925 (week 6) compared to baseline (week 0) and placebo (week 2) were average daily pain (1.09-point reduction from baseline (p=0.0027) and 0.66-point reduction vs. placebo (p=0.0072)), worst daily pain score (0.98-point reduction from baseline (p=0.0169) and 0.61-point reduction vs. placebo (p=0.0360)), total FIQR score (9.6-point reduction from baseline (p=0.0085) and 6.3-point reduction vs. placebo (p=0.0135)) and $PROMIS_{FM}$ Fatigue Profile total score: 5.4-point reduction from baseline (p=0.0081) and 5.6-point reduction vs. placebo (p=0.0049). Taken together, these results warrant further clinical investigation of NYX-2925 in fibromyalgia.

In addition, these data demonstrate that NYX-2925 has predictable PK, including penetration into the CSF and achieves PD effects as measured by changes in sleep and EEG in healthy volunteers and MRI and reported pain in subjects with fibromyalgia.

Overall, NYX-2925 has been safe and well tolerated at oral doses up to 200 mg daily for up to four weeks. Across the studies, there have been few severe treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), or TEAEs leading to study discontinuation, and no deaths. The most commonly reported TEAEs have been headache, diarrhea, upper respiratory tract infection, alanine aminotransferase increased, and arthralgia. No subject reported a SAE while receiving NYX-2925. An NYX-2925-2001 related TEAE leading to study discontinuation (severe headache) was reported, which occurred for a subject receiving daily NYX-2925 10 mg in Study NYX-2925-2001. One NYX-2925-2002 subject had an unrelated TEAE of mild ventricular extrasystoles leading to study discontinuation with onset during the placebo period and was discontinued after 1 dose of NYX-2925 20 mg.

No clinically meaningful changes in vital sign measurements, safety 12-lead electrocardiogram (ECG) results, physical examination findings, Columbia-Suicide Severity Rating scale (C-SSRS), or Sheehan–Suicidality Tracking Scale (S-STS) scores have been observed after a single dose of NYX-2925. Few potentially clinically significant laboratory results were observed during four weeks of treatment in Study NYX-2925-2001; however, these were generally comparable across treatment groups. A single subject in the NYX-2925 10 mg group had elevated clinical laboratory results, including alanine aminotransferase increased and aspartate aminotransferase increased, that met investigative product stopping criteria. On the NYX-2925-2002 study, one (4.8%) subject had a potentially clinically significant GGT result in the NYX-2925 200 mg period and also experienced elevated ALT and AST. These elevations occurred during the NXY-2925 200 mg period and declined following the end of dosing; however, GGT remained above the laboratory reference range at last evaluation, though trending downward.

In summary, NYX-2925 has been sufficiently tested in preclinical studies for safety and tolerability over a wide dose range, with exposures greater than the proposed clinical doses. General toxicology studies in rats and dogs support clinical studies up to and including 13 weeks of daily doses. Clinical results to date indicate that NYX-2925 is safe and well tolerated. The preclinical, Phase 1 and preliminary Phase 2 clinical data support further testing for fibromyalgia in humans.

This study (NYX-2925-2005) is a randomized, double-blind, parallel-group, placebo-controlled study to assess the efficacy and safety of NYX-2925 in subjects with fibromyalgia. NYX-2925 will be provided as capsules for oral administration in strengths of 50 mg NYX-2925 or 100 mg NYX-2925 per capsule.

5. STUDY OBJECTIVES AND ENDPOINTS

5.1. 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

5.2. 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.

5.3. Study Endpoints

5.3.1. Efficacy Endpoints

The primary efficacy endpoint is:

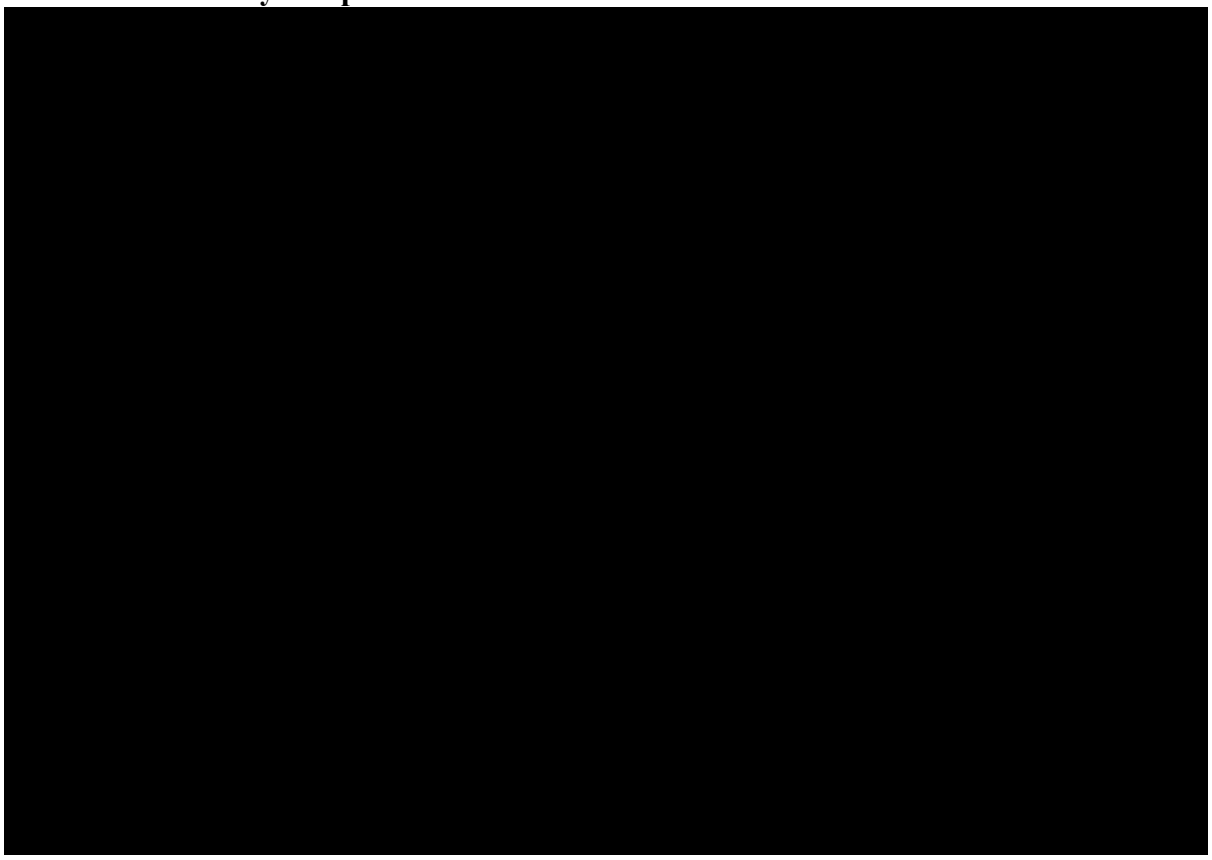
- Change from baseline in the weekly mean of the daily Numerical Rating Scale (NRS) score assessing average pain intensity in the past 24 hours

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 subjects achieving ≥30% 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 Outcomes Measurement Information System – Fibromyalgia ($PROMIS_{FM}$) sleep disturbance score

- Change from baseline to Week 12 in the Patient Reported Outcomes Measurement Information System – Fibromyalgia ($PROMIS_{FM}$) fatigue profile score
- Change from baseline to Week 12 in the Patient Reported Outcomes Measurement Information System – Fibromyalgia ($PROMIS_{FM}$) 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

5.3.2. Other Efficacy Endpoints:



5.3.3. Safety Endpoints

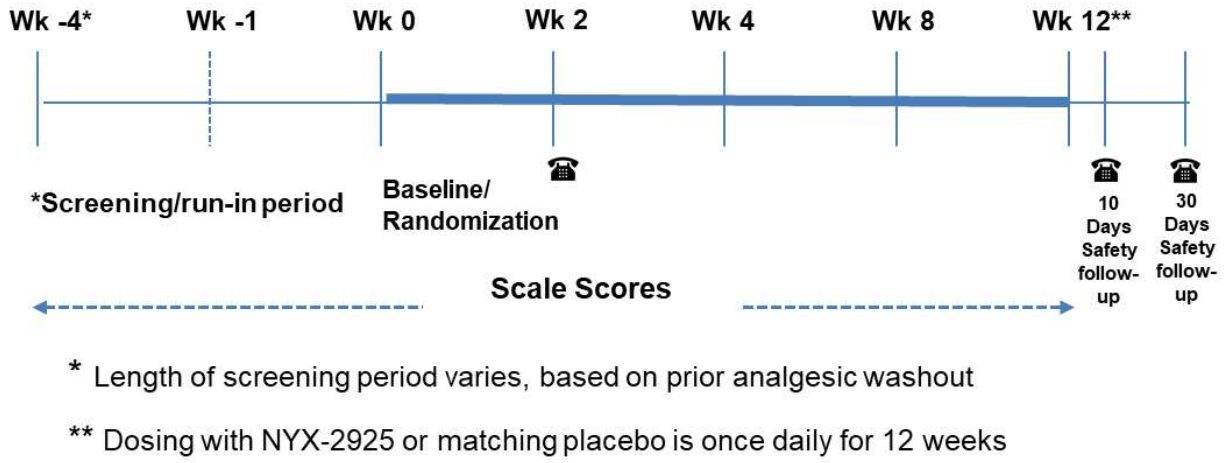
The safety endpoints will include adverse events, (AE), serious adverse events (SAE), discontinuation due to adverse events and the S-STS.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design and Plan: Description

This 13- to 16-week study will include a 1- to 4-week Screening Period, followed by a 12-week double-blind, randomized, placebo-controlled Treatment Period (Figure 1). After completion of the study visits, the site will contact the subjects by telephone within 7-10 days to complete a safety follow-up call. The Investigator, at their discretion, may ask subject to return for an Unscheduled Visit for any safety concerns, abnormal laboratory or ECG findings. A final call will be made to the subject approximately 30 days after the final visit to assess for AE closure and any new SAEs. The study will include up to 52 study sites in the United States.

Figure 1 Study Design



* Length of screening period varies, based on prior analgesic washout

** Dosing with NYX-2925 or matching placebo is once daily for 12 weeks

Table 3: Schedule of Procedures

Study Period	Screening	Baseline	Treatment Period			
Study Week (Day)	1 to 4 weeks[a] (-28 to -1)	Week 0[d] (1 ±2)	Week 2 (14 ±2)	Week 4 (28 ±4)	Week 8 (56 ±4)	Week 12[b] (84 ±4)
Study Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Assessment						
Informed consent prior to any study procedure[c]	X					
Assess inclusion/exclusion criteria	X	X[d]				
APR®/PRR® training via aLearn®[e] [e]	X	X	X[e]	X	X	
Education on appropriate expectations for participation in a clinical study[e]	X	X	X	X	X	X
Patient Global Impression of Severity (PGI-S)	X	X				
American College of Rheumatology (ACR) Fibromyalgia Criteria 2016	X					
Demographic characteristics (age, sex, race, and ethnicity)	X					
Medical history	X					
Height[w]	X					
Body weight[x]	X					X
Vital sign measurements (blood pressure and pulse after sitting or lying supine for at least five minutes)[f]	X	X		X	X	X
Physical examination[g]	X					X
Electrocardiogram after five minutes in supine position[u]	X	X		X	X	X
Urine pregnancy test for females of childbearing potential	X	X		X[h]	X[h]	X[h]
Drug screen[p]	X	X		X	X	X
Obtain samples for chemistry, hematology, and urinalysis[i]	X	X		X	X	X
Discontinue all concomitant analgesic medication[j]	X					
Dispense handheld electronic diary	X					
Return handheld electronic diary						X
Dispense/re-dispense rescue medication (acetaminophen) [k]	X	X		X	X	
Return rescue medication and perform accountability[l]		X		X	X	X

Table 3: Schedule of Procedures (Continued)

Study Period	Screening	Baseline	Treatment Period			
Study Week (Day)	1 to 4 weeks[a] (-28 to -1)	Week 0[d] (1 ±2)	Week 2 (14 ±2)	Week 4 (28 ±4)	Week 8 (56 ±4)	Week 12[b] (84 ±4)
Study Visit	Visit 1	Visit 2	Visit 3[v]	Visit 4	Visit 5	Visit 6
Record average pain intensity[m] and rescue medication use over past 24 hours at bedtime for each day	X	X	X	X	X	X
Randomize eligible subjects		X				
Dispense study drug[o]		X		X	X	
Confirm subject takes first dose of study drug (in the clinic)		X				
Confirm study drug dosing each day via handheld device		X	X	X	X	X
Return study drug and assess compliance[l]			X	X	X	X
Misuse, Abuse, and Diversion Drug Event Reporting System® (MADDERS)[s]			X	X	X	X
Record Daily Sleep Interference Scale (DSIS) each morning[n]	X	X	X	X	X	X
Assess handheld diary compliance		X	X	X	X	
MINI International Neuropsychiatric Interview (MINI)	X					
Fibromyalgia Impact Questionnaire – Revised (FIQR)		X		X	X	X
Patient Reported Outcomes Measurement Information System – Fibromyalgia ($PROMIS_{FM}$)[t]		X		X	X	X
[redacted]						
Patient Global Impression of Change (PGI-C) scale				X	X	X
Sheehan Suicidality Tracking Scale (S-STS)	X	X	X[v]	X	X	X
Concomitant medications[q]	X	X	X	X	X	X
Adverse events[r]	X	X	X	X	X	X
Safety follow-up calls						X[y]

[a] Subjects will discontinue all concomitant analgesic medications taken for pain related to fibromyalgia. Duration of the period will depend upon the analgesic(s) being discontinued, not to exceed 4 weeks. Subjects not taking any concomitant analgesic medications at Visit 1 may directly begin Week -1 of the Screening Period.

[b] ET=Early Termination. Subjects who prematurely discontinue randomized treatment will have Week 12 procedures performed. Diary completion ends the night before the Week 12 visit.

[c] Informed consent includes an additional consent for inclusion in a secure, proprietary, research subject database to screen for protocol violators. The main informed consent document may be executed up to 30 days prior to the screening visit. The date the first screening related activity is completed will be considered the subject's screening date. If the subject does not complete the screening visit within 30 days of signing the informed consent document, the subject must be reconsented.

[d] Verify subject still meets all inclusion criteria and does not meet any exclusion criteria.

[e] Review of these educational materials via the aLearn portal will be repeated for all subjects at each site-based visit, with the exception of the final visit. Training at Visit 3 is per Investigator discretion. Additional refresher training may be administered depending on findings of an ongoing blinded data review (e.g., if pain score variability is increased on a subject or site level).

[f] Vital signs will include blood pressure and pulse after at least five minutes of being seated or lying supine and prior to blood sample collection. Vital signs may be repeated up to three (3) times at screening, per the Investigator's discretion with a minimum interval of five (5) minutes between measurements. All vital signs should be recorded in the subject's source documents with the final measurement of vital signs being entered into the eCRF system.

[g] A complete physical examination will be performed at Visit 1 and will include a comprehensive neurological examination. A brief physical examination will be performed at Visit 6.

[h] If clinically indicated for females of childbearing potential.

[i] Samples will be obtained following an 8-hour fast. Visit 1 tests will include HIV screening, hepatitis B screening, hepatitis C screening, and a thyroid panel (TSH, T_3, T_4 and free T_4). A CRP test will be conducted on each chemistry sample collected.

[j] Analgesic medications discontinued during the Screening Period cannot be restarted until after the Week 12 Visit has been completed (except NSAIDs taken for pain unrelated to FM as outlined in the protocol).

[k] Subjects will be instructed to take no more than 3 g/daily (one to two 500 mg tablets every 6 hours as needed) for pain related to fibromyalgia.

[l] Instruct study subjects to bring all used and unused study drug and rescue medication to each study visit for compliance monitoring. At Visit 3, Study drug & rescue medication use and assessment of compliance will be completed by review of daily use entries in the handheld and by subject interview.

[m] Numerical Rating Scale of pain intensity (0 = no pain to 10 = worst possible pain) will be completed once daily at bedtime. Daily Sleep Interference Scale (DSIS) will be completed once daily upon awakening.

[n] Starting after Visit 1.

[o] Starting after Visit 2. Subjects will be instructed to take one capsule of study drug by mouth once daily and confirm they have taken their study drug for the day via their study-issued handheld device each day.

[p] Urine drug screen kit for local testing.

[q] Includes prior medications taken within the last 30 days.

[r] Adverse events will be collected from the time of study drug administration through the last day of the subject's participation in the study. Serious adverse event reporting will begin at the time informed consent is obtained and will end 30 days after last dose of study drug.

[s] To be completed by Investigators or qualified Subinvestigators when potential abuse-related events are identified and upon the completion of each subject's participation in the study.

[t] Subjects will complete the $PROMIS_{FM}$ sleep disturbance, fatigue profile and physical function short form questionnaires.

[u] Screening ECGs will be collected in triplicate (at least two (2) minutes apart). All other ECGs will be single ECGs.

[v] Visit Three (3) will be completed by telephone or videoconference. The subject will be asked to complete the printed copy of the S-STS given to them at their Baseline Visit while communicating with the site staff. The staff will review the subjects answers to the S-STS and recommend corrections, only where the form has been completed incorrectly. The completed S-STS source document will be mailed back to the clinic or returned at the next study visit to be filed in the subject's chart and entered into the eCRF system.

[w] To be meassured without shoes.

[x] To be obtained with a calibrated scale and subject must remove shoes and bulky layers of clothes.

[y] A safety follow-up call should be completed 7-10 days after Visit 6 completion. Final safety follow-up call to be made 30 (±5 days) days after Visit 6 completion. Investigator may ask subject to return for Unscheduled Visit, as needed.

6.2. Scientific Rationale for Study Design

Double-blind, randomized, placebo-controlled study designs provide unbiased estimates of efficacy and safety. Withdrawal of all concomitant analgesic medication during the Screening Period is expected to reduce intersubject variability in treatment response [Katz 2005; Katz 2015; Data on file] Acetaminophen will be provided as rescue medication. The three-month duration of treatment is considered sufficient to identify clinically important and durable pain relief.

Only masked versions of the protocol will be provided to study sites. The masked versions will obscure the probability of receiving placebo, the treatment period, and the randomization criteria (Section 7.1). Masking is expected to reduce variability in treatment response and to reduce the response to placebo.

6.3. Justification of Dose

The planned dose levels of NYX-2925 are 50 mg and 100 mg per day. Preliminary analysis of the data from the previous Phase 2 study of NYX-2925 in fibromyalgia suggest that after treatment with 20 mg for two weeks followed by 200 mg for two weeks, clinical effects were observed (see Section 4). Over an extended time pDPN tends to become a chronic centralized pain condition [Schreiber 2015, Tesfaye 2013], similar to fibromyalgia. In the Phase 2 study of NYX-2925 in pDPN, the most consistent effects among the pre-planned and post-hoc analyses were observed after administration of 50 mg, and there were also effects seen at the 200 mg dose, although less consistently. The adverse event profile revealed no differences to placebo across the entire dose range in either study. Based on the presumed mechanism of action of NYX-2925, there is no reason to suspect that the dose range for fibromyalgia should be different to that for pDPN. To date no dose level between the four-fold range of 50 mg to 200 mg has been studied in a patient population. Therefore, to obtain a more precise understanding of the dose-response relationship within this range, an additional dose of 100 mg has been selected along with the dose strength of 50 mg to be compared to placebo for the current trial. In the Phase 1 single and multiple ascending dose safety, tolerability and pharmacokinetic study, the PK of NYX-2925 were dose proportional over the dose range tested (50 – 1200 mg). The coefficient of variation (CV%) for exposure remained relatively low across the range (14.0% - 31.5%). Furthermore, a high-fat, high-caloric meal decreased the rate of absorption (delayed T_{max}) and lowered C_{max} by 10%, but had no impact on the extent of exposure (AUC values were comparable), suggesting NYX-2925 can be administered with or without food.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject Inclusion Criteria

Inclusion Criteria: Screening

Inclusion Criteria: Screening

Subjects must meet ALL the following criteria to be enrolled in this study:

1. An Institutional Review Board approved written informed consent and privacy language (Health Insurance Portability and Accountability Act (HIPAA)) authorization must be obtained from the subject prior to performing any study-related procedures. This study may employ electronic informed consent. Electronic or digital signatures (compliant with 21 CFR § 11 regulations for collecting and storing digital signatures) may be captured indicating the patient's willingness to participate in the clinical trial. The use of electronic informed consent supplements the interaction between the participant and the research staff, and it provides an opportunity for remote conduct of study activities in the setting of the COVID-19 Health Emergency.
2. Subject provides separate consent to being included in a research subject database.
3. Subject is ≥18 and ≤75 years of age.
4. Subjects must meet the following 3 conditions described in the 2016 American College of Rheumatology criteria for fibromyalgia [Wolfe 2016]:
    a) Widespread Pain Index ≥7 and Symptom Severity Score ≥5, or the Widespread Pain Index is 4 to 6 and the Symptom Severity Score is ≥9.
    b) Symptoms have been present at a similar level for ≥3 months; and
    c) Pain is generalized and present in at least 4 of 5 regions.
5. Subject has a history of fibromyalgia that was diagnosed >1 year prior to Screening.
6. Subject reports at least moderate pain over the last week, as assessed by PGI-S at Visit 1.
7. Subject agrees to use only rescue medication provided reatment as needed for breakthrough pain related to fibromyalgia.
8. Subject agrees not to initiate or change any non-pharmacologic interventions (including normal daily exercise routines, chiropractic care, physical therapy, psychotherapy, and massage therapy) during the study. Any ongoing non-pharmacologic intervention must be stable for at least 30 days prior to screening.
9. Subject has a body mass index (BMI) ≤40 kg/m^2.
10. Subject's calculated creatinine clearance is ≥60 mL/minute (Cockcroft-Gault formula).
11. Absence of impaired hepatic function characterized by a previous known diagnosis of chronic liver disease, and/or the presence of abnormal serum total bilirubin (TBL), or alanine transaminase (ALT), aspartate transaminase (AST), or alkaline phosphatase (ALP) >1.5x upper limit of normal (ULN) at screening.

12. Except as noted in criteria 10 and 11, subject's clinical laboratory values are within normal limits or deemed not clinically significant by the Investigator.
13. Female subjects of child bearing potential with a negative pregnancy test prior to entry into the study and who are practicing a highly effective method of birth control (e.g., oral or parenteral contraceptives, intrauterine device, barrier [condom and spermicide], abstinence) and who do not plan to become pregnant, breastfeed, or donate ova during the course of the study and for 28 days after the final administration of investigational product.
14. Male subjects should use a highly effective method of birth control and refrain from sexual activity with female sexual partners who do not use a highly effective method of birth control during the study. Male subjects who are not surgically sterilized for at least 90 days prior to screening and sexually active with female partner(s), must agree to use barrier contraception (condom with spermicide) during the study. Subjects must agree to refrain from sperm donation during the study and for 90 days after the final administration of investigational product.
15. Subject has not participated in an interventional study for at least 30 days or has not taken investigational study medication for a period of at least 5 half-lives of the study medication, whichever is longer. Agrees not to participate in another interventional study while on treatment. Eligibility will be reviewed during the study via sponsor participation in a research subject database.
16. Subject has the ability to understand the requirements of the study, abide by the study restrictions, as well as concomitant medications exclusions and agrees to return for the required assessments.

7.2. Subject Exclusion Criteria

Exclusion Criteria:

Subjects who meets ANY of the following criteria will be excluded from the study:

1. Lifetime history of any psychotic and/or bipolar disorder.
2. Subjects with uncontrolled major depressive disorder or generalized anxiety disorder, in the investigator's opinion. (subjects may have been on a stable protocol allowed medication for greater than 60 days prior to screening) or are not expected to remain stable for the duration of the study.
3. Pain due to diabetic peripheral neuropathy, post-herpetic neuralgia, traumatic injury, prior surgery, complex regional pain syndrome, or other source of pain that, in the investigator's opinion, would confound or interfere with the assessment of the subject's fibromyalgia pain or require excluded therapies during the subject's study participation.
4. Pain due to concurrent autoimmune, infectious, or inflammatory disease such as rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease, or other chronic widespread pain condition(s) that may confound fibromyaligia pain reporting.
5. Any impairment, activity or situation that, in the judgment of the Investigator, would prevent satisfactory completion of the study protocol.

6. An untreated endocrine disorder that may confound fibromyalgia assessments.
7. History of severe renal impairment defined by currently receiving hemodialysis or peritoneal dialysis or has undergone a previous renal transplant.
8. Known history of significant cardiovascular condition, such as myocardial infarction within the past year, or moderate to severe congestive heart failure (New York Heart Association [NYHA] Class III and IV); evidence of current uncontrolled cardiac arrhythmias, angina; or electrocardiographic evidence of acute ischemia or clinically significant conduction system anomalies; QTcF >450 msec (males) or >470 msec (females); or uncontrolled hypertension characterized by resting systolic blood pressure >160 mm Hg or resting diastolic >100 mm Hg, or clinically significant hypotension in the judgement of the Investigator as characterized by resting systolic blood pressure <90 mm Hg or resting diastolic blood pressure <60 mm Hg accompanied by symptoms such as lightheadedness, dizziness, and profound fatigue or signs such as irregular heartbeat.
9. Resting pulse rate <45 bpm or >95 bpm.
10. History of Huntington's disease, Parkinson's disease, Alzheimer's disease, multiple sclerosis, or a history of seizures (with the exception of childhood febrile seizures), epilepsy, or stroke.
11. Subject has evidence of any clinically significant, uncontrolled gastrointestinal, endocrinologic, hematologic, immunologic, metabolic, urologic, pulmonary (including uncontrolled, obstructive sleep apnea), neurologic, dermatologic, and/or other major disease (exclusive of fibromyalgia) that may interfere with study participation, as assessed the investigator.
12. Positive serology test for human immunodeficiency virus (HIV) or hepatitis B or C infection, or other ongoing infectious disease that the investigator considers clinically significant.
13. Concomitant use of protocol specified prohibited medications from which subject is unable to wash-out (see Section 8.7 of the protocol for Concomitant Medications Restrictions).
    a. Washout from excluded medication allowed only if the Investigator deems it medically appropriate.
    b. Washout should be completed during screening, with the last dose being at least two (2) weeks prior to randomization (See Section 15.1 of the protocol for Disallowed Analgesic and Other Medications).
14. Sensitivity or allergy to N-methyl-D-aspartate receptor ligands including ketamine, esketamine, amantadine, dextromethorphan, memantine, methadone, dextropropoxyphene and/or ketobemidone.
15. Use of NMDAR-binding drugs (e.g., ketamine, esketamine, amantadine, dextromethorphan, memantine, methadone, dextropropoxyphene, and/or ketobemidone) within 30 days prior to dosing or during the study.
16. Sensitivity to or intolerance to acetaminophen or associated formulation components.

17. Current or recent (within 12 months of screening) history of a substance use disorder including cannabinoid and/or alcohol use disorder as determined using the standard MINI version 7.0.2 for DSM-5™.
18. a. Positive urine drug screen for benzodiazepines or opioids inconsistent with current prescriptions, psychoactive cannabinoids (e.g., marijuana, THC) inconsistent with subject reported use, PCP, cocaine, or amphetamines at Visit 1.

    b. Positive urine drug screen for benzodiazepines inconsistent with protocol specified allowed prescriptions, psychoactive cannabinoids (e.g., marijuana, THC) inconsistent with subject reported use, opioids, PCP, cocaine, or amphetamines at Visit 2.
19. Hypersensitivity or intolerance to multiple medications, in the opinion of the Investigator.
20. Meets the criteria for suicidal intent, plan and/or behavior by scoring 3 or 4 on Questions 2 or 13, or 2 or higher on any Question 1a (only if 1b is coded YES), 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 14 based on the S-STS or who is at significant risk to commit suicide, as assessed by the investigator, at Visit 1 or Visit 2.
21. Planned surgery during study participation.
22. Active malignancy or a history of malignancy (except for treated non-melanoma in-situ skin cancer) within 5 years of screening.
23. Subject has filed for a disability claim or has any pending worker's compensation litigation.
24. Employee, contractor, or volunteer of the study site, CRO, or Aptinyx, or relative of any employee, contractor, or volunteer of the study site, CRO, or Aptinyx or previous randomization into any clinical trial for NYX-2925.
25. Any condition, including serious medical conditions, that could interfere with the ability of the subject to participate in the study or could confound study assessments.
26. History of severe infection with COVID-19 requiring hospitalization, treatment with oxygen or mechanical ventilation, that may interfere with study participation, as assessed the investigator.
27. Any subject with a medical history of COVID-19 infection (positive test) within the last two (2) months, or current symptoms consistent with COVID-19 infection (not tested), e.g. loss of smell, sore throat, cough or fever (2 or more symptoms at the same time), as assessed by the investigator.

Inclusion Criteria: Randomization

Daily pain scores and diary compliance will be transferred into the interactive response technology system, which will be used to assess the criteria for randomization. Subjects whose mean of the daily average pain intensity score during the preceding seven (7) days is within the protocol-defined algorithm and with adequate compliance with daily diary completion will be eligible for randomization.

Waivers to the inclusion or exclusion criteria will **NOT** be allowed.

7.3. Screen Failures

Subjects who sign and date the informed consent form, but who fail to meet the inclusion and do meet any exclusion criteria, will be considered screen failures. The reason(s) for screen failure must be documented by the Investigator. Screen failures may be rescreened, at the Investigator's discretion and will receive a new subject number. Subjects who are randomization ineligible, as determined by IRT, may not be rescreened.

7.4. Subject Withdrawal Criteria

Subjects who withdraw from the Treatment Period will not be replaced. Any subject may withdraw consent at any point during the study. The Investigator may discontinue a subject at any time if it is deemed medically appropriate or for subject noncompliance with study requirements. Subjects who terminate early should return to the clinic for the Early Termination Visit. Subjects may be withdrawn from the study if any of the following criteria are met:

- Occurrence of an adverse event, intercurrent illness, or laboratory abnormality that, in the opinion of the Investigator, warrants the subject's permanent withdrawal from the study for subject safety
- Lack of efficacy
- Subject withdraws consent
- Subject noncompliance
- Lost to follow-up
- Pregnancy
- Sponsor termination of study
- An individual stopping criterion is met
- Other
- Other: COVID-19

7.5. Methods of Birth Control

If heterosexually active and of childbearing potential, female subjects must agree to consistently use a highly effective method of birth control starting at Visit 1, continuing throughout the study, and for 28 days after the last dose of study drug. Methods of highly effective birth control include:

- Oral or parenteral contraceptives
- Intrauterine device (either hormonal or nonhormonal type acceptable)
- Barrier
- Abstinence

Female subjects must agree not to plan to become pregnant or breastfeed starting at Visit 1, during the study and for 28 days after the last dose of study drug. Female subjects must refrain

from donating ova during the study period and for 28 days after final administration of investigational product.

Male subjects must use a highly effective method of birth control and refrain from sexual activity with female sexual partners who do not use a highly effective method of birth control starting at Visit 1 through the last dose of study drug. Male subjects who are not surgically sterilized for ≥90 days prior to Visit 1 and are sexually active with a female partner must use a condom with spermicide during the study. Male subjects must refrain from sperm donation during the study and for 90 days after the final administration of investigational product.

All pregnancies (female subjects and female partners of male subjects) occurring during the study must be followed for information regarding the course of pregnancy, delivery, and condition of the newborn. Follow-up should be provided by the investigator to the Sponsor-designated Medical Monitor in a timely manner. When the newborn is healthy, further follow-up is not necessary.

7.6. Acccurate Pain Reporting and Placebo Response Reduction Training

Prior to recording their first pain score in the handheld diary, each subject will undergo training on Accurate Pain Reporting (APR®) and Placebo Response Reduction (PRR®) via an electronic learning management system, aLearn® [Analgesic Solutions, Wayland, MA]. Subjects will repeat refresher training at subsequent site based study visits, with the exception of the final visit. Refresher training may also be completed remotely via aLearn® at Visit 3, or anytime, per Investigator discretion.

8. STUDY TREATMENT

8.1. Dosing and Administration

This is a double-blind study. Subjects, study personnel and the Sponsor will be blinded to study treatment.

Subjects will be dispensed study drug according to the randomization schedule. A four-week supply of study drug will be dispensed at Weeks 0 (baseline), 4, and 8. Subjects will be instructed to take one capsules of study drug once daily by mouth. The first dose of study drug will be taken in the clinic during the Visit 2 (Week 0). Subjects will be instructed to take study drug once daily throughout the study.

Subjects will be randomized to NYX-2925 50 mg, NYX-2925 100 mg or placebo by mouth, once daily.

Subjects will be dispensed three (3) bottles of acetaminophen to be used as rescue medication at Visit 1. Rescue medication will be dispensed/re-dispensed at the visits identified in Table 3. Rescue medication will consist of 100 count bottle, 500 mg tablets of acetaminophen. Subjects will be instructed to take no more than 3 g/day (one to two 500 mg tablets every 6 hours as needed) for pain associated with fibromyalgia. Rescue medication will be provided by the Sponsor. Use of rescue medication should be reported daily via the study issued- handheld device.

8.2. Study Drug Description, Appearance, Packaging, and Labeling

NYX-2925 is a small molecule, [redacted] that will be provided as capsules for oral administration in a strength of 50 mg and 100 mg NYX-2925 per capsule. Matching placebo capsules will also be provided.

[redacted]

The study drug will be provided in bottles. The labels will include "NYX 2925 Oral Capsules or Placebo," capsule count, bottle number, storage conditions, protocol number, Sponsor name, and investigational use statement. Bottles of study drug will be dispensed at Visit 2/Week 0, Visit 4/Week 4 and Visit 5/Week 8 will include 32 capsules of NYX-2925 50 mg, NYX-2925 100 mg or matching placebo capsules according to the randomization schedule.

Acetaminophen rescue medication will be provided in 100 count bottles containing 500 mg tablets of acetaminophen. The labels will include "Acetaminophen 500 mg tablets", bottle number, protocol number and Sponsor name. Subjects will be instructed to take no more than 3 g/day (one to two 500 mg tablets every 6 hours) as needed for pain related to fibromyalgia. Subjects will be dispensed three (3) bottles of acetaminophen to be used as rescue medication at Visit 1. Additional bottles of rescue medication will be dispensed as needed.

The Sponsor will provide investigative sites with sufficient amounts of study drug and rescue medication to conduct the study.

8.3. Preparation and Handling

The investigative site will receive bottles of blinded study drug. The Investigator may delegate study drug handling to site staff who will dispense bottles of study drug for subject administration according to the interactive response technology system. The interactive response technology system is being utilized to ensure the correct distribution of blinded study drug according to the randomization schedule. The maintenance of treatment randomization codes will be maintained within the IRT system.

The investigative site will receive bottles of acetaminophen rescue medication, and there will be no rescue medication preparation done at the investigative site. The Investigator may delegate rescue medication management to site personnel who will dispense bottles of rescue medication for subject administration according to the IRT system. The IRT system will be utilized to ensure the correct distribution of rescue medication.

8.4. Storage

Study drug should be stored in a locked, limited access location according to the label. The capsules should be stored at 20ºC to 25ºC, with excursions permitted between 15ºC to 30ºC. The investigative site should contact the Sponsor for directions regarding nonpermitted excursions.

Rescue medication should be stored in a locked, limited access location according to the label. The tablets should be stored at 20ºC to 25ºC. The investigative site should contact the Sponsor for direction regarding excursions.

8.5. Accountability

The Investigator or designee at the investigative site will conduct study drug accountability. The investigative site personnel will receive, inspect, and acknowledge condition of study drug and rescue medication; document the amount received, dispensed and returned; and maintain the study drug accountability records. A Sponsor's representative will inspect study drug and accountability records. Site personnel will conduct subject -level accountability, account for and document used/unused study drug and rescue medication, and the site will retain bottles of returned study drug and rescue medication in the investigative site's limited access storage area.

Upon completion or termination of the study and after Sponsor's accountability is completed, all used and unused study drug and containers will be returned to the depot as instructed by the Sponsor's representative. All used and unused rescue medication and containers may be destroyed at the site or returned to the depot as instructed by the Sponsor's representative.

8.6. Treatment Compliance

Site personnel will assess subject compliance with study drug dosing and rescue medication use via pill count and discussion with the subject. In addition, incorrect doses will be documented.

8.7. Concomitant and Excluded Medications

Subjects will discontinue any current analgesic medicationstaken for pain related to fibromyalgia, with the exception of acetaminophen (rescue medication). Rescue medication may be taken for pain related to fibromyalgia only. Stable doses of the benzodiazepines alprazolam and lorazepam will be allowed for the treatment of anxiety. The benzodiazepine receptor agonists, zolpidem (immediate-release) and zaleplon as well as melatonin, ramelteon and low-dose trazodone will be allowed for the treatment of sleep disturbances. Stable doses of serotonin-specific reuptake inhibitors (SSRIs) will be allowed. Intermittment use of triptans for treatment of migraines is permitted.

Concomitant use of antiepileptic drugs, gabapentinoids, mood stabilizers, nonsteroidal anti-inflammatory drugs (NSAIDs [except cardiac preventive low dose acetylsalicylic acid]) outside of infrequent use for pain unrelated to fibromyalgia as described below, systemic corticosteroids, opioid or narcotic analgesics, muscle relaxants, tramadol, injected or topical lidocaine, injected or topical capsaicin, selective norepinephrine reuptake inhibitors (SNRIs), tricyclic (TCAs [except low-dose cyclobenzaprine]), and tetracyclic (TeCAs) antidepressants, monoamine oxidase inhibitors (MAOIs), psychostimulants, sodium oxybate, benzodiazepines (except alprazolam or lorazepam), barbiturates, or NMDA receptor ligands (e.g., ketamine, esketamine, amantadine, dextromethorphan [except low dose intermittent use for cough] memantine, methadone, dextropropoxyphene or ketobemidone) is prohibited.

A positive urine drug screen for benzodiazepines or opioids inconsistent with current prescriptions, psychoactive cannabinoids (e.g., marijuana, THC) inconsistent with subject reported use, PCP, cocaine or amphetamines is exclusionary at Visit 1.

A positive urine drug screen for benzodiazepines inconsistent with protocol specified allowed prescriptions, psychoactive cannabinoids (e.g., marijuana, THC) inconsistent with subject reported use, opioids, PCP, cocaine or amphetamines is exclusionary at Visit 2.

If it is questionable whether a medication(s) falls into the category of excluded medications named above, the Investigator should review the medication with the Sponsor prior to the enrollment of the subject. Washout from excluded medication for fibromyalgia is allowed only if the Investigator deems it is medically appropriate. The washout must be completed within the duration of the Screening Period with the last dose being at least two (2) weeks prior to randomization (See Section 15.1 of the protocol for Disallowed Analgesic and Other Medications).

Subjects will be dispensed acetaminophen to be used as rescue medication and will be instructed to take no more than 3 g/day (one to two 500 mg tablets every 6 hours as needed) for pain related to fibromyalgia. Rescue medication will be provided by the Sponsor.

For pain unrelated to fibromyalgia, subjects may use a nonsteroidal anti-inflammatory drug (NSAID) for up to two (2) days during a seven (7) day period. If the need for analgesics exceeds this period, the patient should call the Investigator to evaluate the cause of pain and the course of action. If a subject requires a NSAID for pain unrelated to fibromyalgia, the medication should be recorded as a concomitant medication and the adverse event must be recorded in the eCRF.

Medications used within 30 days prior to screening through the end of treatment in this study must be documented in the source documents and on the corresponding electronic case report form (eCRF).

9. STUDY ASSESSMENTS AND PROCEDURES

9.1. Screening Assessments

9.1.1. Medical History

Medical history will be documented based on subject report and investigator's assessment.

9.1.2. American College of Rheumatology Fibromyalgia Criteria

The 2016 American College of Rheumatology Fibromyalgia Criteria is a patient survey that is used as a diagnostic tool for fibromyalgia. The diagnostic criteria for fibromyalgia are met by the following 3 conditions [Wolfe 2016]:

- Widespread Pain Index ≥7 and Symptom Severity Score ≥5, or the Widespread Pain Index is 4 to 6 and the Symptom Severity Score is ≥9.
- Symptoms have been present at a similar level for ≥3 months; and
- Pain is generalized and present in at least 4 of 5 regions.

All subjects will be assessed for widespread pain symptoms using these criteria.

9.1.3. Mini-International Neuropsychiatric Interview (MINI)

The MINI is designed as a brief structured diagnostic interview to meet the need for a short but accurate structured psychiatric interview for multicenter clinical trials. The standard MINI version 7.0.2 for DSM-5 will be used in this study to assess the 17 most common disorders in mental health. The disorders investigated are the most important to identify in clinical and research settings. The disorders were selected based on current prevalence rates of 0.5% or higher in the general population in epidemiology studies [Sheehan 1998].

9.2. Efficacy Assessments

9.2.1. Numeric Rating Scale of Pain Intensity (NRS)

The NRS of pain intensity is a unidimensional, segmented numeric version of the visual analog scale. A subject selects a whole number (0 to 10) that best indicates the intensity of his/her pain. The format consists of a horizontal line which is anchored by terms defining pain levels, where 0 represents no pain and 10 represents worst possible pain.

Subjects will report, at bedtime, their average pain intensity during the past 24 hours using the 11-point NRS.

9.2.2. Daily Sleep Interference Scale (DSIS)

The DSIS was developed to quantify sleep interference due to pain. The DSIS is a single item measure that is completed by patients once a day (upon awakening) to accurately capture variability in sleep interference due to pain on a daily basis, thus minimizing recall bias. The DSIS has an 11-point response scale that asks patients to ‘‘Select the number that best describes how much your pain has interfered with your sleep during the past 24 hours.’’ Response options range from 0 (Did not interfere with sleep) to 10 (Completely interfered with sleep/unable to sleep due to pain). The DSIS is designed to be used in a patient daily diary that patients fill out upon awakening each morning [Vernon 2008].

9.2.3. Fibromyalgia Impact Questionnaire – Revised (FIQR)

The FIQR is an updated version of the Fibromyalgia Impact Questionnaire, which is an assessment of the physical functioning, work status, depression, anxiety, morning tiredness, pain, stiffness, fatigue, and well-being in fibromyalgia subjects measured over the period of one week. The FIQR differs from the Fibromyalgia Impact Questionnaire in that it includes questions on memory, tenderness, balance and environmental sensitivity as well as modified function questions [Bennett 2009].

9.2.4. Patient Reported Outcomes Measurement Information Systems – Fibromyalgia PROMIS$_{FM}$ – Fatigue Profile– Short Form

The PROMIS$_{FM}$ fatigue profile is a 16-question instrument that has four 4-item short forms that examine the intensity of the impact of fatigue in social, cognitive, and motivation subdomains [Kratz 2016].

9.2.5. Patient Reported Outcomes Measurement Information Systems – Fibromyalgia PROMIS$_{FM}$ – Sleep Disturbance – Short Form

The PROMIS$_{FM}$ Sleep Disturbance short form is an 8-item instrument that assesses sleep disturbance in subjects 18 years and older [Yu 2011].

9.2.6. Patient Reported Outcomes Measurement Information Systems – Fibromyalgia PROMIS$_{FM}$ – Physical Function – Short Form

The PROMIS$_{FM}$ physical function – short form measures the self-reported performance of physical activities including dexterity, walking or mobility and the ability to complete activities of daily living [Driban 2015].

9.2.7. [redacted]

[redacted]

9.2.8. Patient Global Impression of Severity (PGI-S)

PGI-S is a global index used to rate the severity of a specific condition (a single-state scale), on which (1) corresponds to “no pain” , two (2) corresponds to “mild” , three (3) corresponds to “moderate” and four (4) corresponds to “severe”.

9.2.9. Patient Global Impression of Change (PGI-C)

The PGI-C allows subjects to rate the change in the disease state from study initiation to specific time points during the study or at the end of the study. It provides the subject’s impression of overall change since beginning the study on a 7-point scale on which one (1) corresponds to “very much improved”, four (4) corresponds to “no change” and seven (7) corresponds to “very much worse”.

9.3. Safety Assessments

9.3.1. Safety Parameters

Refer to the Table 3 (Schedule of Procedures) or Section 10 (Schedule of Procedures) for time points.

9.3.2. Vital Sign Measurements

Each assessment includes blood pressure and pulse after at least five (5) minutes of being seated or lying supine, and prior to blood sample collection. Vital signs may be repeated up to three (3) times at screening, per the Investigator’s discretion. There should be a minimum of five (5) minutes of rest allotted in between measurements. All vital signs should be recorded in the

subject's source documents, with the final measurement of vital signs being entered into the eCRF system.

9.3.3. Physical Examination

A complete physical examination will include assessment of the following body systems: head, eyes, ears, nose, and throat, lymph nodes, neurologic, respiratory, cardiovascular, gastrointestinal, musculoskeletal, dermatologic systems and extremities.

The complete physical examination at Visit 1 will include a comprehensive neurological examination of the following components: cranial nerves, muscle strength and tone, sensory function, coordination, gait, reflexes and mental status.

The brief physical examination may be completed at Week 12 or the Early Termination Visit.

For measuring weight, a calibrated scale with appropriate range and resolution will be used. Subjects must remove shoes and bulky layers of clothing.

Height will be measured without shoes.

9.3.4. Electrocardiogram

Triplicate electrocardiograms will be collected at screening after five (5) minutes of supine rest and prior to blood sample collection, if possible. There should be a minimum of a two minute interval between ECGs. The device will be a Spaulding (Spaulding Medical, West Bend, WI) electrocardiogram device that acquires a 12-lead electrocardiogram . The electrocardiogram data will submitted to the designated electrocardiogram laboratory cardiologists for measurements and diagnoses.

The Investigator or qualified Subinvestigator will review all electrocardiogram interpretations and interval duration measurements for clinical significance. Standard electrocardiogram parameters will be measured. Clinically significant, abnormal 12-lead electrocardiograms should be repeated. Clinically significant electrocardiogram changes should be recorded as an adverse event.

The Spaulding electrocardiogram device should be used for all assessments during the study unless it is nonoperational, in which case another electrocardiogram may be performed locally and transmitted to Spaulding for central reading via printout.

9.3.5. Clinical Laboratory Assessments

Blood samples for serum chemistry and hematology will be obtained after an eight-hour fast.

The study investigator should monitor subjects during the study for signs of hepatic abnormality potentially meeting the stopping criteria (Section 11).

The investigator will review clinical laboratory test results as they become available, for determination and documentation of clinical significance (if there are out of range values). The investigative site will contact the medical monitor for any liver function test results that potentially meet the stopping criteria. Possibly drug-related or clinically significant abnormal values of uncertain causality must be repeated. Persistent abnormal laboratory values should be followed at the investigator's discretion. Abnormal liver function tests (specified in Section 11) must be repeated within 48-72 hours.

Hematology assessments will include hemoglobin, hematocrit, red blood cell count, white blood cell count, differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) and platelet count.

Chemistry assessments will include glucose, calcium, electrolytes (sodium, potassium, bicarbonate, chloride), phosphorus, blood urea nitrogen (BUN), creatinine, albumin, total protein, magnesium, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase, gamma-glutamyl transferase (GGT), albumin, total bilirubin, direct bilirubin, indirect bilirubin, uric acid, and C-reactive protein (CRP). A thyroid panel (TSH, T3, T4, and free T4) will also be collected at Visit 1.

Qualitative urinalysis will include pH, specific gravity, glucose, ketones, protein, blood, leukocyte esterase, urobilinogen, nitrites, and reflex microscopy.

Abnormal clinical laboratory tests at screening may be repeated, on a case by case basis, after consultation with the Medical Monitor.

Hepatitis B screening will include both the hepatitis B surface antigen (HBsAg) and the hepatitis B core antibody (HBcAb) testing. If HBsAg and HBcAb are both positive, the subject is not eligible. Additional testing for Hepatitis B surface antibody (HBsAb) will be done in case of a positive test result in subjects for either HBsAg or HBcAb, but not both. Subjects positive for HBcAb and negative for HBsAg, but also negative for hepatitis B surface antibody are not eligible for entry into the study. In addition, if either HBsAg or HBcAb are positive, a confirmatory HBV DNA reflex test will be completed. If the HBV DNA test is positive, the subject will not be eligible.

A history of or a positive test result at Screening for the hepatitis C virus antibody indicating ongoing infection will result in confirmatory testing for hepatitis C_mRNA. Subjects with negative hepatitis C_mRNA will be eligible for entry into the study.

A screening test for HIV will be completed. If the screening test for the HIV antibody is positive, a confirmatory test will be performed.

Female subjects of childbearing potential will receive urine pregnancy tests (human chorionic gonadotropin) at Visit 1, Visit 2, and Visit 6. Testing may be performed at other visits, if clinically indicated.

The urine drug panel will include benzodiazepines, psychoactive cannabinoids (e.g., marijuana, THC), opioids, PCP, cocaine, and amphetamines.

9.3.6. Sheehan Suicidality Tracking Scale (S-STS)

The standard version of the S-STS [Sheehan 2014] is a 16-item scale that assesses the seriousness of suicidality phenomena on a Likert-type scale (0 to 4) ranging from 0 = not at all to 4 = extremely. It also assesses the frequency of key phenomena and the overall time spent in suicidality. The standard version is available in identical clinician- and subject-rated formats. The S-STS accommodates a wide range of time frames. In clinical trials, the frequently used variants are “in the past week”, “in the past month”, “since the last visit”, “lifetime look back”, and “in the past day”.

Suicidality identified after baseline will be recorded as an adverse event.

9.3.7. Abuse and Diversion Assessment

Potentially aberrant drug behavior (i.e., misuse and abuse-related events) will be identified, assessed, and quantified using MADDERS (Analgesic Solutions, Wayland, MA), which consists of a set of forms completed by Investigators or qualified Subinvestigators when potential abuse-related events are identified and upon the completion of each subject's participation in the study. Potential abuse-related events will be adjudicated by an independent committee [Smith 2017; Treister 2016].

Any misuse and abuse-related events will be recorded as adverse events.

9.4. Safety and Pharmacovigilance

9.4.1. Adverse Events – Relationship to Study Drug

An adverse event is any untoward, undesired, unplanned clinical event in the form of signs, symptoms, disease, or laboratory or physiological observations occurring in a human being participating in a clinical study with an Aptinyx study drug, regardless of causal relationship.

Laboratory abnormalities are not considered adverse events unless they are associated with clinical signs or symptoms or require medical intervention. However, a laboratory abnormality (eg, a clinically significant change detected on clinical chemistry, hematology, or urinalysis results) that is independent from the underlying medical condition and requires medical or surgical intervention, or leads to study drug interruption or discontinuation, must be considered an adverse event.

The causality of each AE should be assessed and classified by the Investigator as "related" or "not related." An adverse event is considered related if there is a reasonable possibility that the event may have been caused by the study drug under investigation (i.e., there are facts, evidence, or arguments to suggest possible causation). There is also a timely relationship to the administration of the investigational drug and the event follows a known pattern of response for which no alternative cause is present.

Not Related

- There is no reasonable possibility that the study drug under investigation may have caused the event. The event is obviously explained by another cause or the time of occurrence of the AE is not reasonably related to administration of the study medication.

Related

- There is a reasonable possibility that study drug under investigation caused the event (i.e., there are facts, evidence, or arguments to suggest possible causation). There is also a timely relationship to the administration of the investigational drug and the event follows a known pattern of response for which no alternative cause is present.

When an assessment is not provided, the event will be treated as related for purposes of regulatory reporting.

9.4.2. Recording Adverse Events

A "preexisting" condition is one that is present before study drug dosing and is reported as part of the subject's medical history. Pre-existing conditions should be reported as an adverse event only if the frequency, intensity, or character of the pre-existing condition worsens during the course of the study. Adverse events will be collected from the time ofstudy drug administration through the last day of the subject's participation in the study.

Subjects should be instructed to report all potential adverse events to the Investigator and should be queried in a nonleading manner, without specific prompting (e.g., "How are you feeling?"). The site study staff should assess emerging symptoms of dissociative reaction similar to those caused by *N*-methyl-D-aspartate antagonists, including memory impairment, disturbance in time, body or environmental perception, stilted speech, emotional withdrawal, impaired coordination, motor retardation, bizarre reasoning or illusory experiences in any sensory perception, or confused state; such symptoms may be captured as adverse events.

To avoid vague, ambiguous, or colloquial expressions, all adverse events should be recorded in standard medical terminology rather than in the subject's own words. Each adverse event will also be described in terms of duration (start and stop date), severity, relationship to study drug, action(s) taken, and outcome. Diagnoses (rather than symptoms) should be recorded wherever possible.

9.4.3. Reporting Adverse Events

All adverse events must be documented, evaluated, and reported in the source documents and eCRF. Adverse events will be collected from the time of study drug administration through the last day of the subject's participation in the study. Follow-up of AEs must be conducted in accordance with the investigative site's normal practice. Ongoing adverse events should be followed to a satisfactory resolution in the Investigator's opinion. Subjects should be instructed to report all adverse events to the Investigator. In addition, the Investigator should seek to elicit any clinical or objective reactions by specific questioning (e.g., "How have you been feeling?") and as appropriate by examination. Information on all adverse events should be recorded on the eCRF. All clearly related signs, symptoms, and results of diagnostic procedures performed in relation to an adverse event should be grouped together and recorded as a single diagnosis.

9.4.3.1. Severity of Adverse Events

All adverse events will be assessed for severity, using the following general grading scale:

Mild: Transient or mild discomfort (<48 hours); no medical intervention/therapy required.

Moderate: Mild to moderate limitation in activity – some assistance may be needed; no or minimal medical intervention/therapy required.

Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy, required hospitalization possible.

Life threatening: Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization, or hospice care probable.

When changes in the severity of an adverse event occur more frequently than once a day, the maximum severity for the experience that day should be noted. If the severity category changes

over a number of days, then those changes should be recorded separately (with distinct onset dates).

9.4.3.2. Action Taken for Adverse Events

For each reported adverse event, an Investigator must document the action taken according to the following criteria:

- No action
- Concomitant medication
- Hospitalization or prolongation of hospitalization
- Study discontinued
- Nondrug therapy
- Other (specify)

The Investigator must also document the action taken with study drug (as a result of a given adverse event) according to the following criteria:

- Dose not changed
- Study drug interrupted
- Study drug withdrawn
- Not applicable
- Unknown

9.4.3.3. Outcome for Adverse Events

Adverse events should be followed until resolution. For each reported adverse event, the Investigator must document the outcome according to the following criteria:

- Fatal
- Not recovered/not resolved
- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Unknown

9.5. Serious Adverse Events

Serious adverse event reporting will begin at the time informed consent is obtained and will end 30 days after the last dose of study drug. SAEs must be reported to the sponsor or designee using the provided form either by email or fax to the following email address or fax number, respectively:

- [redacted]

- [redacted]

A serious adverse event is any adverse event occurring at any dose that results in any of the following outcomes:

- Death: "Death" is an outcome and is NOT the adverse event. In the event of death, the cause of death should be recorded as the adverse event. The only exception is "sudden death" when the cause is unknown.
- Is a life-threatening experience: Life-threatening adverse events include any adverse drug experience that, in the view of the Investigator, places the subject at immediate risk of death from the reaction as it occurs. It does not include a reaction that, had it occurred in a more serious form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability/incapacity: Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.
- Results in a congenital anomaly/birth defect.
- Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (eg, allergic bronchospasm requiring intensive treatment in an emergency room or at home).

All serious adverse events that result in death or are life threatening, regardless of causal relationship, must be reported to the Sponsor-designated Medical Monitor within 24 hours of the site's knowledge of the event. A copy of the initial serious adverse event report must be received within one (1) business day.

All other serious adverse events or other events reportable to the United States Food and Drug Administration (FDA) and/or IRB will be forwarded to the Sponsor-designated Medical Monitor within one (1) business day.

Any reported cases of COVID-19 that meet the SAE criteria above should be reported as per the protocol's defined SAE process.

The serious adverse event report should provide as much of the required information as is available at the time. The following minimum information is required for reporting a serious adverse event: subject identification, reporting source, and an event outcome. Supplemental information may be transmitted using a follow-up report and should not delay the initial report. Aptinyx or it's representative may contact the investigational site to solicit additional information or to follow-up on the event.

If there is any doubt whether the information constitutes a serious adverse event, the information will be treated as a serious adverse event for the purposes of this protocol. Serious adverse event reporting will begin at the time of consent and will end 30 days after the last dose.

All relevant documentation pertaining to a serious adverse event (eg, additional laboratory tests, consultation reports, discharge summaries, and postmortem reports) will be provided to the Sponsor -designated Medical Monitor in a timely manner. Serious adverse events will be

followed until resolution or return to baseline (when worsening of a pre-existing condition is reported). If a serious adverse event does not return to baseline but reaches a stable situation that is not expected to change, this may be documented on the serious adverse event form.

The Sponsor may break the treatment code for subjects who experience a serious adverse event in order to determine if the individual case or group of cases requires expedited regulatory reporting. Individual treatment codes will be available to limited staff who are responsible to break codes for reporting purposes.

For each SAE, the Investigator and Sponsor will independently assess whether there is a reasonable possibility that the event may have been caused by the study drug ("drug-related"). The Sponsor will evaluate each drug-related SAE to determine if the event was unexpected. If the SAE is assessed to be both drug-related and unexpected, the Sponsor or designee will notify all Investigators, and will report it to the appropriate regulatory authorities as required by applicable local regulations. The Sponsor or designee will report SAEs, including narratives, to the U.S. FDA and local regulatory authorities as required by 21 CFR 312.32 and the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice. The Investigator is responsible for notifying his/her respective IRB.

9.6. Other Reportable Events

All pregnancies occurring during the study must be followed for information regarding the course of pregnancy, delivery, and condition of the newborn. Follow-up should be provided by the Investigator to the Sponsor-designated Medical Monitor in a timely manner. When the newborn is healthy, further follow-up is not necessary. Male subjects must inform the Investigator if their partner becomes pregnant during the study.

10. SCHEDULE OF PROCEDURES

The schedule of procedures is summarized in Table 3.

10.1. Visit 1 and Screening Period (Week -4 to Week -1)

The subject will be asked to provide written, informed consent for this study before any required procedures are performed. This study may employ electronic informed consent. Electronic or digital signatures (compliant with 21 CFR § 11 regulations for collecting and storing digital signatures) may be captured indicating the patient's willingness to participate in the clinical trial. The use of electronic informed consent supplements the interaction between the participant and the research staff, and it provides an opportunity for remote conduct of study activities in the setting of the COVID-19 Health Emergency. Subjects will also be asked by site staff to sign an additional consent for their inclusion a secure, proprietary research subject database. maintained by Verified Clinical Trials (VCT) [Verified Clinical Trials, Garden City, NY]. The database will use partially identified subject information to review subjects' research study history within the database. Subjects who meet any of the following criteria will not be eligible for continued

screening: current enrollment in another study, concurrent screening at another research site, violation of the required number of half-lives of the investigational product of the prior research study, violation of the washout period between studies, incorrect age for the NYX-2925-2005 study, or previous randomization into a clinical trial of NYX-2925. Employees, contractors, or volunteers of the study site, Contract Research Organization (CRO), or Aptinyx, or relatives of any employee, contractor, or volunteer of the study site, CRO, or Aptinyx are not eligible to participate. Serious adverse event collection begins after the informed consent is obtained and adverse event collection begins after study drug administration.

There may be up to three components in the screening period for this study: 1) After providing informed consent, subjects will participate in a screening visit where medical history, concomitant medications, scales, and eligibility to participate will be assessed; 2) Subjects who meet eligibility requirements and are taking an analgesic medication for pain related to fibromyalgia will then be required to discontinue the analgesia from one to four weeks (see Section 15.1 of the protocol for Disallowed Analgesic and Other Medications). Subjects taking no concomitant analgesic medication for their fibromyalgia at Visit 1 may directly begin Week -1 of the Screening Period; 3) During this time, subjects will be provided a handheld device to record their pain and rescue medication use.

After the informed consents are signed, the following procedures and assessments should be completed at Visit 1:

- Demographic characteristics (age, sex, race, and ethnicity)
- Medical history
- Prior (within last 30 days) and concomitant medications
- PGI-S
- S-STS
- [redacted]
- MINI
- Adverse events
- Confirmation that subjects meet the 2016 American College of Rheumatology criteria for fibromyalgia
- Height and body weight
- Vital signs (blood pressure and pulse after sitting or lying supine for at least five minutes)
- Complete physical examination, including comprehensive neurological examination
- Triplicate electrocardiograms after five (5) minutes in supine position with a minimum of a two minute interval between ECGs
- Blood samples for fasting (8 hours) serum chemistry and hematology
- Blood samples for Human immunodeficiency virus (HIV) and hepatitis screening
- Urine sample for urinalysis

- Urine pregnancy test for females of childbearing potential
- Urine drug test

Eligible subjects who meet all inclusion and exclusion criteria will enter the 1- to 4-week Screening Period. The following procedures and assessments will be performed:

- Subjects will discontinue all analgesic treatments for pain related to fibromyalgia, and complete daily pain diaries. The duration of their Screening Period will depend upon the analgesic treatment that is being discontinued, but the total duration of the Screening Period cannot exceed four (4) weeks (see Section 15.1 of the protocol for Disallowed Analgesic and Other Medications). Subjects taking no concomitant analgesic medication may directly begin Week -1 of the Screening Period.
- Subjects will be provided a handheld device for pain reporting and, as a method for ensuring consistency and reliability of pain scoring, subjects will be instructed at all study visits how to record their pain score on the device and rescue medication use. Subjects will be educated at screening and reminded at other visits on appropriate expectations for their participation in a clinical study and the importance of consistently and accurately reporting their pain throughout the study. On each day preceding the Baseline Visit: (Week 0/Visit 2), subjects will record the following on the handheld device:
    - At bedtime: average pain intensity and use of rescue medication during the past 24 hours
    - Upon waking: DSIS
- Subjects will be dispensed acetaminophen to be used as rescue medication and will be instructed to take no more than 3 g/day (one to two 500 mg tablets every 6 hours as needed) for pain related to fibromyalgia.

10.2. Baseline Visit: Week 0/Visit 2

At Week 0 (Visit 2), the following procedures and assessments will be performed/assessed:

- Concomitant medication use
- PGI-S
- S-STS
- Adverse events
- Vital signs (blood pressure and pulse after sitting or lying supine for at least five minutes)
- Electrocardiogram after five minutes in supine position
- Blood samples for fasting (8 hours) serum chemistry and hematology
- Urine sample for urinalysis
- Urine pregnancy test for females of childbearing potential
- Urine drug test

- Rescue medication return, assessment of appropriate use by inventory of returned tablets, as well as by subject interview
- Verify eligibility with inclusion and exclusion criteria

Pain scores reported by subjects during the Screening Period will be evaluated by the IRT system for raw score and for variability among scores after automated transmission of pain scores from the handheld devices to determine randomization eligibility. The IRT system will notify the site if the subject is "Eligible" or "Not eligible." No other information will be provided.

Subjects who continue to meet all entry criteria and are randomized by the interactive response technology system will undergo the following procedures and assessments:

- FIQR
- $PROMIS_{FM}$ (sleep disturbance, fatigue profile, and physical function)
- [redacted]
- Dispensing of study drug – Subjects will take their first dose in the clinic. They will be instructed to take the study drug daily and confirm they have taken study drug in the handheld device each day.
- Re-dispensing/dispensing of rescue medication – Subjects will be reminded not to exceed 3 g/day (one to two 500 mg tablets every 6 hours as needed) for pain related to fibromyalgia
- Subjects will be reminded on how to record their pain score on the device and will also be reminded about appropriate expectations for their participation in a clinical study and the importance of consistently and accurately reporting their pain intensity throughout the study. Refresher training of these educational materials will be repeated at each site-based study visit via the aLearn® portal, with the exception of the final visit. On each day until returning to the study site, subjects will record the following on the handheld device:
    - At bedtime: average pain intensity and use of rescue medication during the past 24 hours.
    - Upon waking: DSIS and confirm when study drug has been taken
- The subject will be given a printed copy of the study specific S-STS to take home and complete during the Week 2 (Visit 3) telephone or videoconference visit.

10.3. Treatment Period

10.3.1. Week 2/Visit 3

Week 2/Visit 3, will be conducted via telephone or videoconference. The following procedures and assessments will be completed:

- Concomitant medication use
- S-STS – The subject will be asked to complete the printed copy of the S-STS given to them at their Baseline Visit while communicating with the site staff. The staff will review the subject's answers to the S-STS and recommend corrections, only where the

form has been completed incorrectly. The completed S-STS source document will be mailed back to the clinic or returned at the next study visit to be filed in the subject's chart and entered into the eCRF system.

- Adverse events
- Abuse and diversion assessment (MADDERS)
- Rescue medication appropriate use assessment by review of daily use entries in the handheld and by subject interview
- Study drug use and assessment of compliance by review of daily use entries in the handheld and by subject interview
- Compliance with entry into daily diary of pain intensity
- Subjects will be instructed to take one capsule of study drug by mouth once daily
- Subjects will be reminded not to exceed 3 g/day (one to two 500 mg tablets every 6 hours as needed) for pain related to fibromyalgia
- Subjects will be reminded on how to record their pain on the device and will also be reminded about appropriate expectations for their participation in a clinical study.

On each day until returning to the study site at Week 4/Visit4, subjects will record the following on the handheld device:

  - At bedtime: average pain intensity and use of rescue medication during the past 24 hours.
  - Upon waking: DSIS and confirm when study drug has been taken

- A subject may be asked to return to the clinic, per Investigator discretion, for additional study specific training or examination. Any unscheduled return to the clinic should be entered as an Unscheduled Visit into the eCRF and IRT systems.

10.3.2. Week 4/Visit 4 and Week 8/Visit 5

At Week 4/Visit 4 and Week 8/Visit 5, the following procedures and assessments will be performed/assessed:

- Concomitant medication use
- S-STS
- Adverse events
- Abuse and diversion assessment (MADDERS)
- Vital signs (blood pressure and pulse after sitting or lying supine for at least five minutes)
- Electrocardiogram after five minutes in supine position
- Blood samples for fasting (8 hours) serum chemistry and hematology
- Urine sample for urinalysis

- Urine pregnancy test, if clinically indicated for females of childbearing potential
- Urine drug test
- Rescue medication return, assessment of appropriate use by inventory of returned tablets, as well as by subject interview
- Study drug return and assessment of compliance by inventory of returned capsules, as well as by subject interview
- Compliance with entry into daily diary of pain intensity and rescue medication use
- PGI-C
- FIQR
- $PROMIS_{FM}$ (sleep disturbance, fatigue profile and physical function)
- [redacted]
- Dispensing of study drug – Subjects will be instructed to take one capsule of study drug by mouth once daily
- Re-dispensing/dispensing of rescue medication – Subjects will be reminded not to exceed 3 g/day (one to two 500 mg tablets every 6 hours as needed) for pain related to fibromyalgia
- Subjects will be reminded on how to record their pain score on the device and will also be reminded about appropriate expectations for their participation in a clinical study and the importance of consistently and accurately reporting their pain intensity throughout the study. Review of these educational materials will be repeated for all subjects as refresher training or based on findings of an ongoing blinded data review (e.g., if pain score variability is increased on a subject or site level) via the aLearn® portal. On each day until returning to the study site at Week 8/Visit 5, subjects will record the following on the handheld device:
    - At bedtime: average pain intensity and use of rescue medication during the past 24 hours.
    - Upon waking: DSIS and confirm when study drug has been taken

10.3.3. Week 12/Visit 6/Early Termination Visit

At Week 12/Visit 6, or at the time of early termination from the study, the following procedures and assessments will be performed/assessed:

- Concomitant medication use
- S-STS
- Adverse events
- Abuse and diversion assessment (MADDERS)
- Vital signs (blood pressure and pulse after sitting or lying supine for at least five minutes)
- Electrocardiogram after five (5) minutes in supine position

- Body weight
- Brief physical examination
- Blood samples for fasting (8 hours) serum chemistry and hematology
- Urine sample for urinalysis
- Urine pregnancy test for females of childbearing potential
- Urine drug screen
- Compliance with entry into daily diary of pain intensity, rescue medication use and self-administration of study drug
- FIQR
- PGI-C
- $PROMIS_{FM}$ (sleep disturbance, fatigue profile and physical function)
- [redacted]
- Study drug return and assessment of compliance by inventory of returned capsules, as well as by subject interview
- Rescue medication return and assessment of appropriate use by inventory of returned tablets, as well as by subject interview
- Study-issued handheld device and any other study related materials returned
- After completion of the study visits, the site will contact the subjects by telephone within 10 days to complete a safety follow-up call. The Investigator, at their discretion, may ask subject to return for an Unscheduled Visit for any safety concerns, abnormal laboratory or ECG findings.
- A final call will be made to the subject approximately 30 days after the final visit to assess for AE closure and any new SAEs.

11. STOPPING CRITERIA

Subjects will be withdrawn from the treatment period of the study if any of the following laboratory results and symptoms are observed.

- ALT or AST >8xULN – Discontinue subject treatment immediately.
- ALT or AST >5xULN
- ALT or AST >3xULN **and** (TBL >2xULN **or** INR >1.5)
  Discontinue treatment if result is confirmed upon retest (to be done within 48 hours or as soon as feasible).
- ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALT or AST >3xULN that persists for ≥ 4 weeks

If an increase of serum aminotransferase of >3xULN is identified, repeat testing within 48 to 72 hours of all four of the usual serum liver function test measures (ALT, AST, ALP, and TBL) should be conducted to confirm the abnormalities and to determine if they are increasing or decreasing.

12. STATISTICS

12.1. Sample Size Determination

The planned sample size of 300 subjects will provide approximately 80% power for statistical testing with an overall Type I error rate of 0.05.

12.2. Randomization

Pain scores reported by subjects during the Screening Period will be evaluated by the 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 will notify the site if the subject is “Eligible” or “Not eligible.” No other information will be provided.

12.3. Statistical Analysis Plan

The planned statistical analysis methods, including procedures for accounting for missing, unused, and spurious data, will be described in more detail in the Statistical Analysis Plan, which will be finalized prior to study completion. Deviations from the original Statistical Analysis Plan will be described in the final clinical study report.

Descriptive statistics for categorical variables will include the number and percent of subjects with each characteristic. Percentages will be based on the number of subjects with nonmissing values. Descriptive statistics for ordinal and continuous variables will include the number of subjects with nonmissing values, mean, median, standard deviation, minimum value, and maximum value.

All relevant data collected in the eCRF will be shown for each subject in the individual subject data listings.

12.4. Analysis Populations

Safety analyses will be based on the Safety Population, defined as all subjects who receive at least one dose of study drug.

Efficacy analyses will be based on the modified Intent-to-Treat Population, defined as all subjects in the Safety Population with at least one postbaseline assessment of the pain intensity NRS.

12.5. Treatment Group Comparisons

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

- NYX-2925 50 mg
- NYX-2925 100 mg
- Placebo

The following treatment group comparisons will be performed for efficacy:

- NYX-2925 50 mg versus placebo
- NYX-2925 100 mg versus placebo

12.6. Analyses of Efficacy

12.6.1. Primary Efficacy Analysis

The primary efficacy analysis will be performed based on the modified Intent-to-Treat population.

The primary efficacy endpoint is the change from baseline in the weekly mean of the daily NRS score assessing average pain intensity in the past 24 hours. The primary efficacy analysis will evaluate the treatment-policy estimand in the modified Intent-to-Treat population. The treatment-policy estimand combines the improvement (reduction) from Baseline in the weekly mean of the daily NRS score and 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:

1. Population = Subjects meeting the protocol-specified inclusion/exclusion criteria, who received at least one dose of study drug and who have at least one post-baseline assessment of the pain intensity NRS.
2. Subject-level outcome = Change from baseline in the weekly mean of the daily NRS score assessing average pain intensity in the past 24 hours
3. Intercurrent event handling = An intercurrent event is defined as discontinuation of study drug due to an AE or lack of efficacy prior to Week 12. For the analysis, baseline Observation Carried Forward (BOCF) 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).
4. Population-level summary measure = Difference in least squares 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.

For the primary efficacy endpoint, the daily pain intensity NRS score from the handheld device will be averaged for baseline after randomization. Change from baseline will be assessed for

treatment group difference using a mixed model for repeated measures (MMRM) with factors for study site, treatment, week, treatment by week interaction, and including the baseline value of the response variable as a covariate. Line plots displaying the mean weekly NRS scores from Weeks 1 through 12 for each treatment group will be generated. In these plots, the horizontal axis will reflect the study week and the vertical axis will reflect the average pain score.

12.6.2. Sensitivity Analysis

As a sensitivity analysis for the primary efficacy endpoint, an analysis of covariance (ANCOVA) model will be used to assess treatment differences. The model will include factors for study site and treatment and include the baseline value of the response variable as a covariate.

Sensitivity analyses will be performed on the primary endpoint, evaluating the impact of the missing at random (MAR) assumption for missing data. Multiple imputation (MI) techniques based on Pattern Mixture Models (PMM) will be applied as the first sensitivity analysis. This methodology will structure data based on a missingness pattern having a monotone structure. An MI analysis with missing not at random (MNAR) assumption will be applied as the second sensitivity analysis. Placebo group based imputation will be used (i.e. the trajectories of the subjects with missing data on NYX-2925 are assumed to follow the placebo group after discontinuation).

If the primary efficacy analysis significantly favors one or both doses of NYX-2925, a tipping point sensitivity analysis for the primary efficacy endpoint will be conducted. In this analysis, the assumption will be that that data in the NYX-2925 groups are not missing at random. A tipping point based assumption will be used, i.e. the trajectories of the subjects in each of the NYX-2925 groups after withdrawal are assumed to be worse than placebo by an amount of delta. Successively harsher deltas will be imposed on the subjects in the NYX-2925 groups, starting with a mean weekly NRS score increment (increaase) of 0.5 points. The delta will be further increased in steps of 0.5 points (i.e., 1.0, 1.5, 2.0) until the statistical significance is lost, i.e. until the p-value becomes >0.05.

12.6.3. Secondary Efficacy Endpoints

The following secondary endpoints will be analyzed:

- 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 subjects achieving ≥30% 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 Outcomes Measurement Information System – Fibromyalgia ($PROMIS_{FM}$) sleep disturbance score

- Change from baseline to Week 12 in the Patient Reported Outcomes Measurement Information System – Fibromyalgia ($PROMIS_{FM}$) fatigue profile score
- Change from baseline to Week 12 in the Patient Reported Outcomes Measurement Information System – Fibromyalgia ($PROMIS_{FM}$) 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

12.6.4. Other Efficacy Analyses

12.6.5. Multiple Comparisons

The primary efficacy endpoint and primary statistical analysis are protocol specified.

The primary efficacy endpoint and other selected efficacy endpoints will be tested (using MMRM as described above) to preserve the overall Type I error rate.

There will be no other adjustments for multiple comparisons.

12.7. Analyses of Safety

All safety summaries will be descriptive; no statistical testing will be performed.

12.7.1. Adverse Events

A TEAE is defined as an adverse event with an onset that occurs after receiving study drug, or a continuing adverse event diagnosed prior to the date of first dose of study drug that increases in severity after the start of dosing. Adverse events will be categorized by system organ class and preferred term with the Medical Dictionary for Regulatory Activities (MedDRA).

Summary tables for TEAEs will include number and percent of subjects experiencing TEAEs by system organ class and preferred term. If a subject has more than one TEAE that codes to the same preferred term, the subject will be counted only once for that preferred term. Similarly, if a subject has more than one TEAE within a system organ class category, the subject will be counted only once in that system organ class category.

The following TEAE summaries will be provided for the Treatment Period:

- Overall summary of TEAEs
- TEAEs by system organ class and preferred term
- Drug-related TEAEs by system organ class and preferred term
- TEAEs by system organ class, preferred term, and severity
- Serious TEAEs by system organ class and preferred term
- TEAEs leading to study drug discontinuation by system organ class and preferred term

12.7.2. Clinical Laboratory Tests

Mean changes from baseline will be summarized descriptively for each clinical laboratory parameter.

Clinical laboratory results considered clinically important by the Investigator will be identified. Individual results for clinical laboratory tests (serum chemistry, hematology, and urinalysis) outside the normal range will be flagged in the data listings.

Clinical laboratory assessments will be conducted by a central laboratory.

12.7.3. Electrocardiogram

The interpretation of ECG and interval duration measurements by the designated ECG laboratory cardiologists will be reviewed by the Investigator. Clinically significant deteriorations from baseline will be reported and summarized as TEAEs.

12.7.4. Vital Sign Measurements

Mean change from baseline will be summarized descriptively for each vital sign.

12.7.5. Suicidal Ideation

Subjects with suicidal ideation or behavior will be identified with the S-STS.

12.8. Interim Analysis

No interim analysis is planned for this study.

13. ADMINISTRATIVE

13.1. Source Documents

Source documents are defined as the result of original observations and activities of a clinical investigation. Source documents may include, but are not limited to, study progress notes, e-mail correspondences, informed consent forms, clinical laboratory reports, medical histories, hospital records, and drug accountability records. All source documents will be maintained by the Investigator(s) and made available for inspection by Sponsor representatives, the FDA, and other applicable regulatory authorities.

13.2. Study Monitoring

Site visits will be conducted by an authorized Sponsor representative (Site Monitor) to inspect study data, source documents, and eCRFs in accordance with International Council for Harmonisation (ICH) guidelines, Good Clinical Practice (GCP), and local regulations or guidelines. The Monitor will inspect the study data at regular intervals throughout the study to verify adherence to the protocol, as well as completeness, consistency, and accuracy of study data.

Aptinyx is also collecting the impact of COVID-19 on visits (e.g. incomplete or remote visits, dosing interruptions, changes in planned IP dispensation).

The Investigator will permit Sponsor representatives, its third-party vendors, the FDA, and/or respective health authorities to inspect facilities and records relevant to this study.

13.3. Case Report Forms

An eCRF will be used to record all subject data required in this protocol. The eCRF must be completed by designated and trained study personnel. The eCRF will be signed by the Principal Investigator or a Subinvestigator listed on the FDA Form 1572. It is the responsibility of the Principal Investigator to ensure the eCRFs are completed and submitted to Aptinyx (or designee) in an accurate and timely manner. The processing of eCRFs will include an audit trail (to include changes made, reason for change, date of change, and person making the change).

13.4. Protocol Amendment(s)

If a protocol has been filed with regulatory agencies or submitted to an IRB and requires changes, a protocol amendment must be written. The Sponsor will make changes to the protocol. All amendments will be sent to a central IRB on the study sites' behalf, if applicable. Sites using a local IRB are responsible for submitting the amendment for review and approval.

13.5. Audits and Inspections

During the course of the study or after completion of the study, each study site may be subject to an audit by an Aptinyx Quality Assurance Auditor (or an auditor appointed by Aptinyx or its authorized representative) and/or an inspector from the FDA and/or other regulatory authority. Every attempt will be made to notify the Investigator in writing in advance of the audit.

13.6. Institutional Review Board

This protocol, the informed consent document, and all relevant supporting data must be submitted to the IRB for approval. Institutional Review Board approval of the protocol, informed consent documents, any subject-facing materials, and any advertisement used to recruit study subjects must be obtained before the study may be initiated. The IRB must comply with requirements set forth in the Code of Federal Regulations (CFR) part 56.

The Investigator is responsible for keeping the IRB advised of the progress of the study, changes to research activity, unanticipated problems involving risk to human subjects or others and any changes made to the protocol, as deemed appropriate, but in any case, at least once a year. The Investigator is also responsible for notifying the IRB of any significant adverse events or protocol deviations that occur during the study and meet IRB reporting requirements.

The Investigator agrees that he/she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects, as referenced in 21 CFR 312.66.

13.7. Compliance with Regulatory Requirements

This study will be conducted in compliance with the protocol and all regulatory requirements, in accordance with GCP, including ICH Guidelines, and in general conformity with the most recent version of the Declaration of Helsinki.

13.8. Informed Consent

Written informed consent must be obtained from potential study subjects prior to the initiation of any study-related procedures. This study may employ electronic informed consent. Electronic or digital signatures (compliant with 21 CFR § 11 regulations for collecting and storing digital signatures) may be captured indicating the patient's willingness to participate in the clinical trial. The use of electronic informed consent supplements the interaction between the participant and the research staff, and it provides an opportunity for remote conduct of study activities in the setting of the COVID-19 Health Emergency. The informed consent document may be executed up to 30 days prior to the screening visit. The date the first screening related activity is completed will be considered the subject's screening date. If the subject does not complete the screening visit within 30 days of signing the informed consent document, the subject must be reconsented. The original signed informed consent form for each participating subject shall be filed with records kept by the Investigator(s). A copy of the signed informed consent document must be provided to the subject. If applicable, written consent will be obtained using a certified translation. If the informed consent form is revised, subjects actively participating in the study must be reconsented in a timely manner.

13.9. Study File Management

The Investigator is responsible for ensuring that the study files are maintained. The study file will include, but is not limited to, source documents, correspondence, regulatory documents (IRB approvals/correspondence, study logs, FDA 1572 forms, financial disclosures, clinical study material records, study drug accountability records, and medical records).

13.10. Study Completion

Aptinyx requires the following data and materials be completed before a study can be considered terminated or completed: source documents are completed, study drug reconciliation activities are completed, and study procedures and assessments are source verified and completed.

13.11. Confidentiality

Personal study subject data collected and processed for the purposes of this study should be managed by the Investigator and his/her staff with adequate precautions to ensure the confidentiality of personal health information, and in accordance with applicable national and/or local laws and regulations on personal health information protection.

Monitors, auditors, and other authorized agents of Aptinyx, the IRB approving this research and applicable regulatory authorities will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects, to the extent permitted by the law and regulations. In any presentation of the results of this study at meetings or in publications, the subjects' identities will remain confidential.

13.12. Compensation, Insurance, and Indemnity

Information regarding compensation, insurance, and indemnity is addressed in the Clinical Trial Research Agreement.

13.13. Financial Disclosure

The Investigator(s) are responsible for providing financial disclosure(s) in covered clinical studies. Principal Investigators and Subinvestigators are required to disclose applicable financial information, and to promptly update Aptinyx with any relevant changes throughout the study and for one (1) year after study completion.

13.14. Records Retention

According to United States Investigational New Drug regulations (21 CFR 312.62), records and documents pertaining to the conduct of this study and the distribution of study drug including but not limited to source documents, eCRFs, informed consent forms, clinical laboratory test results, and drug inventory records will be retained. These records will be kept on file by the Principal Investigator for two years after a marketing application is approved for the drug for the indication for which it is being studied. If no application is filed or approved, these records must be kept for two years after the investigation has been discontinued and the FDA has been notified. Per ICH guidelines, documents should be retained until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or

contemplated marketing applications in an ICH region, or at least two years have elapsed since the formal discontinuation of clinical development of the study drug. Aptinyx will notify the Investigator when records and documents no longer need to be retained. No study records should be destroyed without prior authorization.

13.15. Publication Policy

The publication policy is outlined in the Clinical Trial Agreement.

14. REFERENCES

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15. APPENDICES

15.1. Disallowed Analgesic and Other Medications*

Washout of the following disallowed analgesics should be completed during screening, with the last dose being at least 2 weeks prior to randomization.

- Tricyclic antidepressants (TCAs)
- Norepinephrine reuptake inhibitors (NRIs), e.g., atomoxetine (Strattera®) and bupropion (Wellbutrin®, Zyban®)
- Serotonin-norepinephrine reuptake inhibitors (SNRIs), eg., milnacipran (Savella), duloxetine (Cymbalta®), venlafaxine (Effexor®), Desvenlafaxine (Pristiq®), levomilnacipran (Fetzima®)
- Anti-epileptics, eg., gabapentin (Neurontin®) and pregabalin (Lyrica®); NMDA receptor ligands
- Opioids
- NSAIDs (except as described in section 8.7)
- Benzodiazepines except alprazolam or lorazepam
- Muscle relaxants
- Acetaminophen or acetaminophen containing therapies for indications other than fibromyalgia
- Topical therapies: topical capsaicin; topical/local anesthetic lidocaine

*Any non-pharmacologic therapies or interventions for treatment of pain that are not on this list needs to be discussed with the Medical Monitor prior to screening (eg., nerve blocks, spinal stimulators, etc).

Subjects must be stable for at least seven (7) days prior to randomization. The "stable" condition is based on investigators' clinical judgment. It means no significant withdrawal effects, and to be stable regarding their pain, i.e., subjects should not be in a flare state with much worse pain than before washout as is common with discontinuation of any drugs but most common with NSAIDs and opioids.

Prohibited medications must not be withdrawn for participation in this study when prescribed for a condition other than pain.