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

Amendment #7

25 June 2021

NCT04146896

INVESTIGATIONAL PRODUCT: NYX-2925
CLINICAL PROTOCOL: NYX-2925-2008

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

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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.

PROCEDURES IN CASE OF EMERGENCY

Table 1 Emergency Contact Information

24-Hour Emergency Medical Contact		
Medical Monitor	[redacted]	[redacted]
Serious Adverse Event Reporting Information		
Email: [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 Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

Study center(s):
Approximately 37 centers in the US

Studied period (years):	**Phase of development:**
Estimated date first subject enrolled: August 2019 Estimated date last subject completed: January 2022 The study period was extended due to the COVID-19 Health Emergency.	2

Objectives:

Primary objective:

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

Secondary objective:

- To assess the effects of NYX-2925 50 mg QD versus placebo on pain characteristics, sleep interference, psychological state, and global improvement.

Methodology:

Study Design

The study will be a 13- to 16-week study, including 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 -1:

Upon Institutional Review Board (IRB) approval of the protocol, subjects 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 to provide 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 of the prior research study, violation of the washout period between studies, incorrect age for the NYX-2925-2008 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 diabetic peripheral neuropathy will then be required to discontinue the analgesic medication. Subjects taking no concomitant analgesic medication for their painful diabetic neuropathy 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 device, each subject will undergo educational training on Accurate Pain Reporting (APR®) and Placebo Response Reduction (PRR®) via an electronic learning management system, aLearn® [Analgesic Solutions, Wayland, MA].

Subjects with Type 2 diabetes who have been on stable antidiabetic medication for at least one (1) month (or have stable glycemic control with diet and exercise alone) and who have been diagnosed with diabetic peripheral neuropathy (DPN) in the lower extremities for at least four (4) years (DPN in the upper extremities is not exclusionary) will be screened for diabetic peripheral neuropathy using the Michigan Neuropathy Screening Instrument (MNSI), and the Masquerading Disorders Tool (MDT). Subject must have presence of pain due to diabetic neuropathy for at least 6 months prior to screening. Subjects 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 completion of the Sheehan-Suicidality Tracking Scale (S-STS), serious adverse event collection which will begin from the time of the informed consent is obtained through 30 days after the last dose of study drug, demographic characteristics, medical history (including history of Type 2 diabetes and history of painful DPN prior (within the last 30 days) and concomitant medications, complete physical examination (with comprehensive neurological examination), triplicate 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 5 minutes), height, body weight, and collection of blood (8 hour fast) samples for hematology, serum chemistry, hemoglobin A1c (HbA1c), triglycerides, human immunodeficiency virus (HIV) screening, hepatitis screening, thyroid panel (TSH, T3, T4 and free T4). and urine sample will be collected for urinalysis testing. Vital signs may be repeated up to three (3) 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 drug screens 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 eligible for 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 neuropathic pain associated with diabetic peripheral neuropathy, 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 concomitant analgesic medication for their painful diabetic neuropathy 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 and rescue medication use on the device. Subjects will also be educated at screening (APR® and PRR® training [Analgesic Solutions, Wayland, MA]) via the aLearn® electronic learning management system and provided refresher training in that portal at all site-based study visits, with the exception of the final visit. Subjects will be reminded at all visits of appropriate expectations around their participation in a clinical study and the importance of consistently and accurately reporting their pain throughout the study. An ongoing blinded data review (e.g., if pain score variability is increased on a subject or site level) will be conducted to monitor these metrics [Analgesic Solutions, Wayland, MA].

Subjects will be dispensed acetaminophen to be used as rescue medication (RM) and will be instructed to take no more than 2 g /day (one to two 500 mg tablets every 6 hours as needed up to 4 tablets total) for DPN related pain.

For pain unrelated to DPN, 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 DPN, the medication should be recorded as a concomitant medication and the adverse event must be recorded in the eCRF.

Beginning at Week - 1, DPN 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, worst pain intensity, average pain upon walking, 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 pain imaginable. 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): MNSI, MDT, PGI-S and S-STS.

Screening Period: Week -1 (as needed)

Subjects taking no concomitant analgesic medication for their painful diabetic neuropathy 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 when the subjects are on site and perform safety assessments prior to randomization.

The appropriate use of rescue medication will be assessed by inventory of the returned tablets, as well as by subject interview. Subjects will be asked a nonleading question to assess potential adverse events. Use of concomitant medications will be documented. Additional procedures during Visit 2 will include the S-STS, an ECG, and vital signs (blood pressure and pulse after sitting or lying supine for at least five (5) minutes). Blood (8 hour fast) samples will be collected for hematology, serum chemistry, and urine sample will be collected for urinalysis testing. Subjects will undergo drug screens 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 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 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 drug daily throughout the study. Acetaminophen will be dispensed/re-dispensed for use as rescue medication for DPN related pain; and instructions on not to exceed 2 g/day (one to two 500 mg tablets every 6 hours as needed up to 4 tablets total) 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, worst pain intensity, average pain upon walking, and usage of rescue medication over the past 24 hours into their study-issued handheld devices every night. Every morning upon awakening, subjects will complete the DSIS and confirm they have taken their study drug in the past 24 hours via their study-issued handheld device. Pain diary compliance will be reviewed at each study visit by the study staff, and reporting instructions will be reinforced. Subjects will be reminded of appropriate expectations around their participation in a clinical study and the importance of consistently and accurately reporting their pain intensity throughout the study. Each subject will undergo educational training on Accurate Pain Reporting (APR®) and Placebo Response Reduction (PRR®) via an electronic learning management system, aLearn® [Analgesic Solutions, Wayland, MA]. Review of these educational materials will be repeated for all subjects as refresher training This training is mandatory prior to randomization and at each site-based visit, with the exception of the final visit. An ongoing blinded data review (e.g., if pain score variability is increased on a subject or site level) will be conducted to monitor these metrics [Analgesic Solutions, Wayland, MA].

The following scales will be completed at the Baseline Visit (Visit 2): Brief Pain Inventory for Diabetic Peripheral Neuropathy (BPI-DPN), the Norfolk Quality of Life Questionnaire - Diabetic Neuropathy (QOL-DN), Patient Global Impression of Severity (PGI-S), Pain Catastrophizing Scale (PCS) and Sheehan – Suicidality Tracking Scale (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 study staff via telephone or videoconference at the end of Week 2 (Visit 3) for assessment of compliance with study drug, rescue medication use and diary entries. The appropriate use of study drug and rescue medication will be assessed by subject interview. Subjects will be instructed to continue to take one capsule of study drug by mouth once daily throughout the study.

The subject will be reminded not to exceed 2 g/day (one to two 500 mg tablets every 6 hours as needed up to 4 tablets total) for DPN related pain. Pain diary compliance will be reviewed by the study staff, and reporting instructions will be reinforced. Adverse events will be assessed by asking 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.

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. 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.

Subjects will be instructed to continue entering their average pain intensity, worst pain intensity, average pain upon walking, and rescue medication use over the past 24 hours into their study-issued handheld devices every night, and to complete the DSIS and confirm they have taken their study drug in the past 24 hours via their study-issued handheld device every morning upon awakening. Subjects will be reminded of appropriate expectations around their participation in a clinical study and the importance of consistently and accurately reporting their pain throughout the study. APR®/PRR® training via the aLearn® portal is optional per investigator discretion for Week 2/Visit 3.

The following scales will be completed at the Week 2 (Visit 3) visit via telephone or videoconference: S-STS.

Treatment Period: Week 4/Visit 4

Subjects will return to the clinic at the end of Week 4 (Visit 4) 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 be dispensed a four-week supply of study drug. Subjects will be instructed to continue to take one capsule of study drug by mouth once daily. Rescue medication will be dispensed/re-dispensed to the subject with instructions not to exceed 2 g/day (one to two 500 mg tablets every 6 hours as needed up to 4 tablets total) for DPN related pain.

Pain diary compliance will be reviewed by the study staff, and reporting instructions will be reinforced. Adverse events will be assessed by asking 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.

Additional procedures during Visit 4 will include S-STS and vital signs (blood pressure and pulse after sitting or lying supine for at least five (5) minutes). Blood (8 hour fast) samples will be collected for hematology, serum chemistry and urine sample will be collected for urinalysis testing. Subjects will undergo drug screens 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, worst pain intensity, average pain upon walking, and rescue medication use over the past 24 hours into their study-issued handheld devices every night, and to complete the DSIS and confirm they have taken their study drug in the past 24 hours via their study-issued handheld device every morning upon awakening. 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, with the exception of the final visit. This review will be completed in the aLearn portal®. An ongoing blinded data review (e.g., if pain score variability is increased on a subject or site level) will be conducted to monitor these metrics [Analgesic Solutions, Wayland, MA].

The following scales will be completed at Week 4 (Visit 4): BPI-DPN, Patient Global Impression of Change (PGI-C), QOL-DN and S-STS.

Treatment Period: Week 8/Visit 5

Subjects will return to the clinic at the end of Week 8 (Visit 5) 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 be dispensed a four-week supply of study drug. Subjects will be instructed to continue to take one capsule of study drug by mouth once daily throughout the study. Rescue medication will be dispensed/re-dispensed to the subject with instructions not to exceed 2 g/day (one to two 500 mg tablets every 6 hours as needed up to 4 tablets total) for DPN related pain. Pain diary compliance will be reviewed by the study staff, and reporting instructions will be reinforced. Adverse events will be assessed by asking 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.

Additional procedures during Visit 5 will include S-STS and vital signs (blood pressure and pulse after sitting or lying supine for at least five (5) minutes). ECG would be conducted. Blood (8 hour fast) samples will be collected for hematology serum chemistry, and urine sample will be collected for urinalysis testing. Subjects will undergo drug screens 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, worst pain intensity, average pain upon walking, and rescue medication use over the past 24 hours into their study-issued handheld devices every night, and to complete the DSIS and confirm they have taken their study drug in the past 24 hours via their study-issued handheld device every morning upon awakening. Subjects will be reminded of 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 within the aLearn® portal at each site-based visit, with the exception of the final visit. An ongoing blinded data review (e.g., if pain score variability is increased on a subject or site level) will be conducted to monitor these metrics [Analgesic Solutions, Wayland, MA].

The following scales will be completed at Week 8 (Visit 5): PGI-C and S-STS.

Treatment Period: Week 12/Visit 6 or Early Termination Visit
During Week 12 (Visit 6) or 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 other 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 nonleading question. Misuse and abuse-related events will be assessed using MADDERS. Use of concomitant medications will be documented. Additional Visit 12/Early Termination Visit procedures include S-STS and vital signs (blood pressure and pulse after sitting or lying supine for at least five (5) minutes). Body weight will be measured, a brief physical examination will be performed, and ECG would be conducted. Blood (8 hour fast) samples will be collected for hematology, serum chemistry, HbA1c, and urine sample will be collected for urinalysis testing. Subjects will undergo drug screens using a local urine testing kit.
Female subjects of childbearing potential will be tested for pregnancy using a local urine testing kit.

The following scales will be completed at the Week 12 (Visit 6)/Early Termination Visit: BPI-DPN, PGI-C, QOL-DN, PCS and S-STS.

A safety follow-up telephone call will be made to the subject within 7-10 days and then approximately 30 days after Visit 6 / Week 12 to assess for any AE/SAE closure and any newly reported SAEs.

Number of subjects:
Approximately 204 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. Consent to being included in a research subject database.
3. Subject is ≥18 and ≤75 years of age.
4. Diagnosis of Type 2 Diabetes.
5. At least moderate pain intensity over the last week as assessed by PGI-S at Visit 1.
6. Hemoglobin A1c (HbA1c) ≤11% (measured at Visit 1).
7. Stable use of diabetic medications beginning 1 month prior to Visit 1 (adequate glycemic control with diet and exercise alone is also permitted).
8. Diabetic peripheral neuropathy, of symmetrical nature and in lower extremities for ≥4 years (DPN in the upper extremities is not exclusionary).
9. Presence of pain due to diabetic neuropathy for at least 6 months prior to screening.
10. Total score of ≥4 on the Michigan Neuropathy Screening Instrument.
11. Body mass index ≤40 kg/m^2.
12. Absence of impaired hepatic function. Impaired hepatic function is characterized by a previous known diagnosis of chronic liver disease, and/or 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.
13. Calculated creatinine clearance ≥60 mL/minute (Cockcroft-Gault formula).
14. Fasting triglycerides ≤600 mg/dL.
15. Except as noted in criteria 12-14 above, clinical laboratory values must be within normal limits, or deemed not clinically significant by the investigator.
16. 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.
17. 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.
18. Has not participated in an interventional study for at least 30 days or has not taken 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.
19. Ability to understand the requirements of the study, abide by the study restrictions, as well as concomitant medications exclusions, and agree to return for the required assessments.
20. 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.

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 criteria will NOT be allowed.

Exclusion Criteria:

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

1. Current diagnosis of a major psychiatric disorder (including schizophrenia and/or bipolar disorder), including those who have required an antipsychotic (e.g., aripiprazole, asenapine, cariprazine, clozapine, lurasidone, olanzapine, quetiapine, risperidone, ziprasidone) or mood stabilizer (e.g., lithium, carbamazepine, lamotrigine, valproate) for a psychiatric condition in the past year, or subjects who have had a major depressive episode (MDE) in the past 6 months. Subjects with major depressive disorder (MDD), generalized anxiety disorder (GAD) or panic disorder who have been on stable medication for the past 3 months (and are expected to remain stable for the duration of the study) and whose condition is currently well-controlled may be included.
2. Pain that cannot be clearly differentiated from, or could interfere with, the assessment of peripheral diabetic neuropathy, as measured by the Masquerading Disorders Tool at Visit 1.
3. Neurologic disorders unrelated to diabetic neuropathy (e.g., phantom limb from amputation), skin condition in the area of neuropathy that could alter sensation (e.g., plantar ulcer), or other painful conditions (e.g., arthritis) that, in the judgment of the investigator, could interfere with reporting of pain due to diabetic neuropathy.
4. History of hypoglycemia that disturbed consciousness, or ketoacidosis requiring hospitalization within the past 3 months.
5. History of severe renal impairment defined by renal dialysis or peritoneal dialysis or has undergone renal transplant.
6. 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), or 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.
7. Pulse rate <45 bpm or >90 bpm.
8. 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.
9. Positive serology test result for HIV or current hepatitis B or C infection, or other ongoing infectious disease that the investigator considers clinically significant.
10. Concomitant use of protocol specified prohibited medications and 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).
11. Current or recent (within 12 months of screening) history of a substance use disorder including cannabinoid use disorder.

12.
   a. Visit 1: 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. Visit 2: 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.
13. Sensitivity or allergy to, or concomitant use of N-methyl-D-aspartate receptor ligands including ketamine, esketamine, amantadine, dextromethorphan, memantine, methadone, dextropropoxyphene, lamotrigine, and/or ketobemidone.
14. Use of NMDAR-binding drugs (e.g., ketamine, esketamine, amantadine, dextromethorphan, memantine, methadone, dextropropoxyphene, lamotrigine, and/or ketobemidone) within 30 days prior to dosing or during the study. Use of high concentration capsaicin patch within 3 months prior to screening; use of lidocaine patch within 1 month prior to screening.
15. Sensitivity to or intolerance to acetaminophen or associated formulation components.
16. Hypersensitivity or intolerance to multiple medications, in the opinion of the investigator.
17. Amputations of lower extremities (toe(s) amputation is allowed).
18. 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.
19. Planned surgery during study participation.
20. Active malignancy or a history of malignancy (except for treated non-melanoma in-situ skin cancer) within 5 years of screening.
21. 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.
22. 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. Presence of an exclusionary masquerading disorder in the Masquerading Disorders Tool (MDT) assessment.
23. 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 diabetes) that may interfere with study participation, as assessed the investigator.
24. Previous randomization in current or previous NYX-2925 clinical trials.
25. Subject has filed for a disability claim or has any pending worker's compensation litigation.
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.

Waivers to the exclusion criteria will NOT be allowed.

Test product, dose and mode of administration, batch number:

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

Reference therapy, dose and mode of administration, batch number:
Placebo, oral capsules, single capsule once daily by mouth

Rescue medication:
Acetaminophen, up to 2 g/day, as needed for DPN related pain. To be dispensed in 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 diabetic peripheral neuropathy need to be discontinued with the last dose taken at least two (2) weeks prior to randomization.
Maintenance: Twelve (12) weeks of blinded treatment with either NYX-2925 50 mg QD or placebo QD.

Criteria for evaluation:
Efficacy endpoint:
Primary efficacy endpoint:

- Change from baseline in the weekly mean of the daily Numeric Rating Scale (NRS) score assessing average pain intensity related to DPN in the past 24 hours.

Secondary efficacy endpoints:

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

Other efficacy endpoints:

[redacted]

Sample Size:

The planned sample size is a total of 204 randomized subjects. This will provide approximately 80% power using statistical testing with an overall Type I error rate of 0.05.

Statistical methods:

Safety analyses will be based on the Safety Population, which is 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, which is defined as all subjects in the Safety Population with at least one 1 post baseline assessment of the weekly mean of pain intensity NRS.

Change from baseline will be assessed for treatment group differences 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.

An analysis of covariance (ANCOVA) model with fixed factors of study site and treatment, and using the baseline value as a covariate will be done as a sensitivity analysis.

Change in the weekly mean of the daily NRS score assessing average pain intensity in the past 24 hours from baseline will be assessed using analogous MMRM and ANCOVA models as described for the primary efficacy endpoint above. Change from baseline for weekly mean NRS score for average pain upon walking and worst daily pain, DSIS, BPI-DPN, PCS and QOL-DN 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, percentage of subjects achieving ≥50% reduction, and sustainability of ≥30% and ≥50% reduction in the weekly mean NRS average pain intensity related to DPN will be summarized.

The number of days to the first ≥30% reduction and number of days to the first ≥50% reduction in the weekly mean NRS average pain intensity related to DPN will be assessed for treatment group differences using the log-rank test or other applicable 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 results 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 or specialist term	Explanation
AE	Adverse Event
ALT	alanine transaminase
ANCOVA	analysis of covariance
ALP	alkaline phosphatase
APR®	Accurate Pain Reporting®
AST	aspartate transaminase
BPI-DPN	Brief Pain Inventory for Diabetic Peripheral Neuropathy
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
CRO	contract research organization
CRP	C-reactive protein
CSF	cerebrospinal fluid
DPN	diabetic peripheral neuropathy
DSIS	Daily Sleep Interference Scale
DSM-5™	Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
GAD	generalized anxiety disorder
GCP	Good Clinical Practice
Glx	glutamate + glutamine metabolites
HbA1c	hemoglobin A1c, glycated hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
IRT	interactive response technology
MADDERS	Misuse, Abuse, and Diversion Drug Event Reporting System®

Abbreviation or specialist term	Explanation
MDD	major depressive disorder
MDE	major depressive episode
MDT	Masquerading Disorders Tool
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
MNSI	Michigan Neuropathy Screening Instrument
NF	National Formulary
NMDAR	*N*-methyl-D-aspartate receptor
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NRS	Numeric Rating Scale
NYHA	New York Heart Association
PCS	Pain Catastrophizing Scale
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PRR®	Placebo Response Reduction®
QOL-DN	Norfolk Quality of Life Questionnaire - Diabetic Neuropathy
SAE	serious adverse event
S-STS	Sheehan-Suicidality Tracking Scale
TBL	total bilirubin
T_3	Triiodothyronine
T_4	Thyroxine
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
TSH	thyroid stimulating hormone
VCT	Verified Clinical Trials
ULN	upper limit of normal
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 small molecule interacts with *N*-methyl-D-aspartate receptors (NMDARs) through a novel binding domain and acts as 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, 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].

The central nervous system modulates the experience of pain in people with neuropathic pain, with the rostroventralmedial 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. The prevalence of neuropathic pain is approximately 8% in the population in the United States [Gilron 2015; Toth 2013; Bouhassira 2008]. Individuals suffering from neuropathic pain, irrespective of the underlying disorder, currently have limited treatment options available.

Current treatment options predominantly include antidepressants and antiepileptics. These therapies have shown some efficacy in treating neuropathic pain symptoms, although for a large proportion of patients, treatment is insufficient.

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 1 hour. NYX-2925 is rapidly eliminated from plasma, with an apparent terminal elimination half-life in the range of 4 to 5 hours in rats and 1 to 2 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 August 2020, the clinical development program for NYX-2925 includes 3 completed Phase 1 studies in healthy volunteers, 1 completed Phase 2 study in subjects with diabetic peripheral neuropathy (DPN), 1 completed Phase 2 study in subjects with fibromyalgia. NYX-2925 exposure in these studies includes 154 healthy volunteers, 229 subjects with DPN, and 22 subjects with fibromyalgia. There is also one ongoing Phase 2 study in subjects with fibromyalgia.

In Phase 2 Study NYX-2925-2001, 300 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). NYX-2925 did not significantly affect average pain scores in adult subjects with neuropathic pain associated with DPN. However, numerical improvements in pain intensity were observed in subjects taking NYX-2925 compared with placebo, especially for subjects with long-standing disease who were not using a 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.

Exploratory efficacy analyses of NYX-2925 (20 and 200 mg) compared to placebo have also been performed in Phase 2 Study NYX-2925-2002 in 22 subjects with fibromyalgia. Clinically meaningful and nominally statistically significant improvements were observed in pain, fatigue, the overall intensity of fibromyalgia symptoms and their impact on function. NYX-2925 demonstrated antinociceptive activity in neuroimaging evaluations. Pharmacodynamic results from this study revealed that NYX-2925 reduced glutamate + glutamine (Glx) levels within the posterior insula, a region previously implicated in pain processing in fibromyalgia.

Pharmacokinetic analysis revealed that absorption of NYX-2925 was relatively rapid; peak concentrations were achieved within 2 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 7 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.

Overall, NYX-2925 appears to be safe and well tolerated at oral doses up to 200 mg daily for up to 4 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, arthralgia, abdominal distension, anxiety, and eructation. 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 NYX2925 20 mg.

No clinically meaningful changes in vital sign measurements, safety 12-lead electrocardiogram (ECG) results, physical examination findings or suicidality have been observed after a single dose of NYX-2925. Few potentially clinically significant laboratory results were observed during 4 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 Phase 2 clinical data support further testing in patients with painful peripheral diabetic neuropathy.

This study (NYX-2925-2008) is a randomized, double-blind, placebo-controlled study to assess the efficacy and safety of NYX-2925 in subjects with neuropathic pain associated with diabetic peripheral neuropathy. NYX-2925 will be provided as capsules for oral administration in a strength of 50 mg NYX-2925 per capsule.

5. STUDY OBJECTIVES AND ENDPOINTS

5.1. Primary Objective

The primary objective of this study is:

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

5.2. Secondary Objective

The secondary objective of the study is:

- To assess the effects of NYX-2925 50 mg QD versus placebo on pain characteristics, sleep interference, 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 Numeric Rating Scale (NRS) score assessing average pain intensity related to DPN in the past 24 hours.

The secondary efficacy endpoints are:

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

5.3.2. Other Efficacy Endpoints

[redacted]

5.3.3. Safety Endpoints

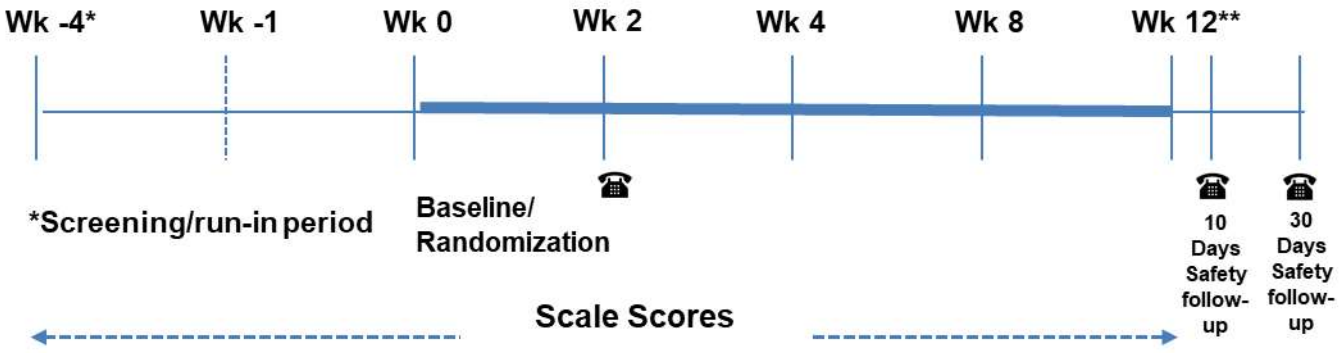
The safety endpoints will include adverse events and serious adverse events, discontinuation due to AE and the S-STS.

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; 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 37 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

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

Upon Institutional Review Board (IRB) approval of the protocol, 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 to provide 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 of the prior research study, violation of the washout period between studies, incorrect age for the NYX-2925-2008 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 diabetic peripheral neuropathy will then be required to discontinue the analgesic medication. Subjects taking no concomitant analgesic medication for their painful diabetic

neuropathy 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 this time, subjects will be provided a handheld device to record their pain and rescue medication use. Prior to recording their first pain score in the handheld device, 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 with Type 2 diabetes who have been on stable antidiabetic medication for at least one (1) month (or have stable glycemic control with diet and exercise alone) and who have been diagnosed with DPN in the lower extremities for at least four (4) years (DPN in the upper extremities is not exclusionary) will be screened for diabetic peripheral neuropathy using the Michigan Neuropathy Screening Instrument (MNSI) and the Masquerading Disorders Tool (MDT). Subjects must have presence of pain due to diabetic neuropathy for at least 6 months prior to screening. Subjects must report at least "moderate pain" over the last week, as assessed by the Patient Global Impression of Severity (PGIS) at the screening visit. Additional procedures during Visit 1 will include the completion of the Sheehan-Suicidality Tracking Scale (S-STS); serious adverse event collection which will begin from the time of informed consent is obtained through 30 days after the last dose of study drug, demographic characteristics, and medical history (including history of Type 2 diabetes and history of painful DPN, prior (within the last 30 days) and concomitant medications, complete physical examination (with comprehensive neurological examination), triplicate 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 (5) minutes), height, body weight, and collection of blood (8 hour fast) samples for hematology, serum chemistry, hemoglobin A1c (HbA1c), triglycerides, human immunodeficiency virus (HIV) screening, hepatitis screening, and urine sample will be collected for urinalysis. Vital signs may be repeated up to three (3) 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 urine drug screens 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 eligible for 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, including those being taken for neuropathic pain associated with diabetic peripheral neuropathy. 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 not taking concomitant analgesic medications 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 how to record their pain and rescue medication use on the device. Each subject will undergo

educational training on Accurate Pain Reporting (APR®) and Placebo Response Reduction (PRR®) via an electronic learning management system, aLearn® [Analgesic Solutions, Wayland, MA] Subjects will be educated at screening and reminded at other study visits on appropriate expectations around their participation in a clinical study and the importance of consistently and accurately reporting their pain throughout the study. This training is mandatory prior to randomization and at each site-based visit, with the exception of the final visit. An ongoing data review (e.g., if pain score variability is increased on a subject or site level) will be conducted to monitor these metrics [Analgesic Solutions, Wayland, MA].

Subjects will be dispensed acetaminophen to be used as rescue medication and will be instructed to take no more than 2 g /day (one to two 500 mg tablets every 6 hours as needed up to 4 tablets total) for DPN related pain.

For pain unrelated to DPN, 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 DPN, the medication should be recorded as a concomitant medication and the adverse event must be recorded in the eCRF. Beginning at Week -1, DPN 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, worst pain intensity, average pain upon walking, 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 pain imaginable. 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): MNSI, MDT, PGI-S and S-STS.

Screening Period: Week -1 (as needed)

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

Baseline Visit: Week 0/Visit 2

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

The appropriate use of rescue medication will be assessed by inventory of the returned tablets, as well as by subject interview. Subjects will be asked a nonleading question to assess potential adverse events. Use of concomitant medications will be documented. Additional procedures during Visit 2 will include the S-STS, an ECG, and vital signs (blood pressure and pulse after sitting or lying supine for at least five (5) minutes). Blood (8 hour fast) samples will be collected for hematology, serum chemistry, and urine sample will be collected for urinalysis testing. Subjects will undergo drug screens 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, PCP, opioids,

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 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 doses of oral NYX-2925 50 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 drug daily throughout the study. Acetaminophen will be dispensed/re-dispensed for use as rescue medication for DPN related pain; and instructions on not to exceed 2 g/day (one to two 500 mg tablets every 6 hours as needed up to 4 tablets total) will be reinforced.

Adverse events will be collected 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, worst pain intensity, average pain upon walking, and usage of rescue medication 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 in the past 24 hours via their study-issued handheld device. Pain diary compliance will be reviewed by the study staff, and reporting instructions will be reinforced. Subjects will be reminded of appropriate expectations around their participation in a clinical study and the importance of consistently and accurately reporting their pain intensity throughout the study. Each subject will undergo educational training on Accurate Pain Reporting (APR®) and Placebo Response Reduction (PRR®) via an electronic learning management system, aLearn® [Analgesic Solutions, Wayland, MA].Review of these educational materials will be repeated for all subjects within the aLearn® platform at each site-based visit, with the exception of the final visit. An ongoing blinded data review (e.g., if pain score variability is increased on a subject or site level) will be conducted to monitor these metrics [Analgesic Solutions, Wayland, MA].

The following scales will be completed at the Baseline Visit (Visit 2): Brief Pain Inventory for Diabetic Peripheral Neuropathy (BPI-DPN), the Norfolk Quality of Life Questionnaire - Diabetic Neuropathy (QOL-DN), Patient Global Impression of Severity (PGI-S)Pain Catastrophizing Scale (PCS) and Sheehan – Suicidality Tracking Scale (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 study staff via telephone or videoconference at the end of Week 2 (Visit 3) for assessment of compliance with study drug, rescue medication use and diary entries. The appropriate use of study drug and rescue medication will be assessed by subject interview. Subjects will be instructed to take one capsule of study drug by mouth once daily. Rescue medication, if required should not exceed 2g/day (one to two 500 mg tablets every 6 hours as needed up to 4 tablets total for DPN 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 the Misuse, Abuse, and Diversion Drug Event Reporting System® (MADDERS [Analgesic Solutions, Wayland, MA]). Use of concomitant medications will be documented.

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. 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.

Subjects will be instructed to continue entering their average pain intensity, worst pain intensity, average pain upon walking, 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 in the past 24 hours via their study-issued handheld device. Subjects will be reminded of 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 within the aLearn® platform at each site-based visit, with the exception of the final visit. An ongoing blinded data review (e.g., if pain score variability is increased on a subject or site level) will be conducted to monitor these metrics [Analgesic Solutions, Wayland, MA].

The following scales to be completed at Week 2 (Visit 3) visit via telephone or videoconference: S-STS.

Treatment Period: Week 4/Visit 4

Subjects will return to the clinic at the end of Week 4 (Visit 4) 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 be dispensed a four-week supply of study drug.

Subjects will be instructed to take one capsule of study drug by mouth once daily. Rescue medication will be dispensed/re-dispensed to the subject with instructions not to exceed 2g/day (one to two 500 mg tablets every 6 hours as needed up to 4 tablets total) for DPN related pain.

Pain diary compliance will be reviewed by the study staff, and reporting instructions will be reinforced. Adverse events will be elicited by asking the subject a nonleading question. Misuse and abuse-related events will be assessed using MADDERS (Analgesic Solutions, Wayland, MA). Use of concomitant medications will be documented. Additional procedures during Visit 4 will include S-STS and vital signs (blood pressure and pulse after sitting or lying supine for at least five (5) minutes). Blood (8 hour fast) samples will be collected for hematology, serum chemistry, and urine sample will be collected for urinalysis testing. Subjects will undergo drug screens 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, PCP, opioids, cocaine or amphetamines, will not be allowed to continue in the study. 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, worst pain intensity, average pain upon walking, and rescue medication use over the past 24 hours into their study-issued handheld device every night and to complete the DSIS and confirm they have taken their study drug in the past 24 hours via their study-issued handheld device in morning. Subjects will be reminded of 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 within the aLearn portal at each site-based visit, with the exception of the final visit. An ongoing blinded data review (e.g., if pain score variability is increased on a subject or site level) will be conducted to monitor these metrics [Analgesic Solutions, Wayland, MA].

The following scales will be completed at Week 4 (Visit 4): BPI-DPN, Patient Global Impression of Change (PGI-C), QOL-DN and S-STS.

Treatment Period: Week 8/Visit 5

Subjects will return to the clinic at the end of Week 8 (Visit 5) 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 be dispensed a four-week supply of study drug.

Subjects will be instructed to take one capsule of study drug by mouth once daily. Rescue medication will be dispensed/re-dispensed to the subject with instructions not to exceed 2g/day (one to two 500 mg tablets every 6 hours as needed up to 4 tablets total) for DPN related pain.

Pain diary compliance will be reviewed by the study staff, and reporting instructions will be reinforced. Adverse events will be elicited by asking the subject a nonleading question. Misuse and abuse-related events will be assessed using MADDERS (Analgesic Solutions, Wayland, MA). Use of concomitant medications will be documented.

Additional procedures during Visit 5 will include S-STS and vital signs (blood pressure and pulse after sitting or lying supine for at least five (5) minutes). ECG would be conducted. Blood (8

hour fast)) samples will be collected for hematology, serum chemistry, and urine sample will be collected for urinalysis testing. Subjects will undergo drug screens 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, PCP, opioids, cocaine or amphetamines, will not be allowed to continue in the study. 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, worst pain intensity, average pain upon walking, 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 in the past 24 hours via their study-issued handheld device. Subjects will be reminded of 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 visit, with the exception of the final visit. An ongoing blinded data review (e.g., if pain score variability is increased on a subject or site level) will be conducted to monitor these metrics [Analgesic Solutions, Wayland, MA].

The following scales will be completed at Week 8 (Visit 5): PGI-C and S-STS.

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

During Week 12 (Visit 6) or 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 other 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 nonleading question. Misuse and abuse-related events will be assessed using MADDERS (Analgesic Solutions, Wayland, MA).

Use of concomitant medications will be documented. Additional procedures during Visit 6/Early Termination Visit will include S-STS and vital signs (blood pressure and pulse after sitting or lying supine for at least five (5) minutes). Body weight will be measured, a brief physical examination performed, and ECG would be conducted. Blood (8 hour fast) samples will be collected for hematology, serum chemistry, HbA1c, and urine sample will be collected for urinalysis testing. Female subjects of childbearing potential will be tested for pregnancy using a local urine testing kit. Subjects will a undergo drug screens using a local urine testing kit.

The following scales will be completed at the Week 12 (Visit 6)/Early Termination Visit: BPI-DPN, PGI-C, QOL-DN, PCS and S-STS.

A safety follow-up telephone call will be made to the subject within 7-10 days and then approximately 30 days after week 12/final visit to assess for any AE/SAE closure and any newly reported SAEs.

The schedule of assessments is provided in Table 3.

Table 3 Schedule of Procedures

Study Period	Screening	Baseline	Treatment Period			
Study Week (Day)	1 to 4 weeks[a] (-28 to -1)	Week 0 (1± 2)[b]	Week 2 (14 ± 2)	Week 4 (28 ± 4)	Week 8 (56 ± 4)	Week 12/ ET[b] (84 ± 4)
Study Visit	Visit 1	Visit 2	Visit 3[w]	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]	X	X	X	X	X	
Education on appropriate expectations around participation in a clinical study[e]	X	X	X	X	X	
Michigan Neuropathy Screening Instrument (MNSI)	X					
Masquerading Disorders Tool (MDT)	X					
Demographic characteristics (age, sex, race, and ethnicity)	X					
Medical history	X					
Height[t]	X					
Body weight [t,u]	X					X
Vital signs (blood pressure and pulse after sitting or lying supine for at least 5 minutes) [f]	X	X		X	X	X
Physical examination [g]	X					X
Triplicate electrocardiograms (3 separate ECGs) with a minimum of 2 mins gap between each ECG.[v]	X					
Electrocardiogram (ECG) after at least 5 minutes in supine position		X			X	X
Urine pregnancy test for females of childbearing potential[h]	X	X		X	X	X
Urine Drug screens [i]	X	X		X	X	X
Obtain samples for hematology, chemistry, and urinalysis [j]	X [j]	X		X	X	X [j]
Discontinue all concomitant analgesic medications[k]	X					
Dispense handheld electronic diary	X					

Study Period	Screening	Baseline	Treatment Period			
Study Week (Day)	1 to 4 weeks[a] (-28 to -1)	Week 0 (1± 2)[b]	Week 2 (14 ± 2)	Week 4 (28 ± 4)	Week 8 (56 ± 4)	Week 12/ ET[b] (84 ± 4)
Study Visit	Visit 1	Visit 2	Visit 3[w]	Visit 4	Visit 5	Visit 6
Return handheld electronic diary						X
Dispense/re-dispense rescue medication (acetaminophen) [l]	X	X		X	X	
Return rescue medication and perform accountability [m]		X		X	X	X
Record average pain intensity, worst pain intensity, average pain upon walking and rescue medication use over past 24 hours at bedtime for each day [n]	X	X	X	X	X	X
Record Daily Sleep Interference Scale (DSIS) each morning [o]	X	X	X	X	X	X
Assess handheld diary compliance		X	X	X	X	X
Randomize eligible subjects		X				
Dispense study drug		X		X	X	
First dose of study drug (in the clinic)		X				
Confirm daily study drug dosing in past 24 hours each morning[p]		X	X	X	X	X
Return study drug and assess compliance[m]				X	X	X
Pain Catastrophizing Scale (PCS)		X				X
Brief Pain Inventory for Diabetic Peripheral Neuropathy (BPI- DPN)		X		X		X
Norfolk Quality of Life Questionnaire – Diabetic Neuropathy (QOL-DN)		X		X		X
Patient Global Impression of Severity (PGI-S)	X	X				
Patient Global Impression of Change (PGI-C)				X	X	X
Sheehan-Suicidality Tracking Scale (S-STS)	X	X	X[w]	X	X	X
Misuse, Abuse, and Diversion Drug Event Reporting System® (MADDERS) [r]			X	X	X	X
Concomitant medications	X[q]	X	X	X	X	X
Adverse events[s]	X	X	X	X	X	X
Safety follow-up calls						X[x]

a) Subjects will discontinue all concomitant analgesic medications taken for pain related to diabetic peripheral neuropathy. 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. An ongoing blinded data review (e.g., if pain score variability is increased on a subject or site level) will be conducted to monitor these metrics [Analgesic Solutions, Wayland, MA].

f) Vital signs will include blood pressure and pulse after sitting or lying supine for at least five (5) minutes, 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 the Visit 6/Early Termination Visit.

h) If clinically indicated for females of childbearing potential.

i) Urine drug screen kit for local testing.

j) Samples will be obtained following an 8 hour fast. Visit 1 tests will include HbA1c, triglycerides, HIV screening, hepatitis B screening, hepatitis C screening, CRP, and a thyroid panel (TSH, T3, T4 and free T4). Visit 6 (Week 12)/Early Termination Visit tests will include HbA1c. A CRP test will be conducted on each chemistry sample collected.

k) Analgesic medications discontinued during the Screening Period cannot be restarted until after the Week 12 visit.

l) Subjects will be instructed to take no more than 2 g/daily (one to two 500 mg tablets every 6 hours as needed up to 4 tablets total) for DPN related pain.

m) Instruct study participants to bring all used and unused study drug and rescue medication to each visit for compliance monitoring.

n) Numeric Rating Scale of pain intensity (0 = no pain to 10 = worst pain imaginable) will be completed once daily at bedtime. DSIS will be completed upon waking.

o) Starting after Visit 1.

p) 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 in past 24 hours via their study-issued handheld device upon awakening in morning.

q) Includes prior medications taken within the last 30 days.

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

s) 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 the last dose of study drug..
t) BMI will be calculated based on height and body weight.
u) Weight to be obtained with a calibrated scale with appropriate range and resolution. Subject must remove shoes and bulky layers of clothes
v) Screening ECGs will be collected in triplicate (at least two (2) minutes apart). All other ECGs will be single ECGs.
w) 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 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.
x) 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 medications during the Screening Period is expected to reduce intersubject variability in treatment response [Katz 2005; Katz 2015; Data on file]. The three-month duration of treatment is considered sufficient to identify clinically important pain relief. As described in Section 4, although NYX-2925 did not meet the primary endpoint in the prior Phase 2 study, the observed trends toward improved changes in average pain intensity suggest that NYX-2925 has the potential to mitigate neuropathic pain in patients who are not using a concomitant analgesic medication and with long-standing disease (i.e., ≥4 years).

Only masked versions of the protocol will be provided to study sites. The masked versions will obscure the probability of receiving placebo 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

In the first Phase 2 study, the most consistent effects of NYX-2925 were observed at the 50 mg dose in pre-planned and post-hoc analyses, as described in Section 4. The adverse event profile revealed no differences to placebo across the entire dose range. Thus, 50 mg has been selected to be compared to placebo for the current study. In the Phase 1 single and multiple ascending dose safety, tolerability and pharmacokinetic study, 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

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

1. An Institutional Review Board (IRB) 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. Consent to being included in a research subject database.
3. Subject is ≥18 and ≤75 years of age.
4. Diagnosis of Type 2 Diabetes.
5. At least moderate pain intensity over the last week as assessed by PGI-S at Visit 1.
6. Hemoglobin A1c (HbA1c) ≤11% (measured at Visit 1).
7. Stable use of diabetic medications beginning 1 month prior to Visit 1 (adequate glycemic control with diet and exercise alone is also permitted).
8. Diabetic peripheral neuropathy, of symmetrical nature and in lower extremities for ≥4 years (DPN in the upper extremities is not exclusionary).

9. Presence of pain due to diabetic neuropathy for at least 6 months prior to screening.
10. Total score of ≥4 on the Michigan Neuropathy Screening Instrument.
11. Body mass index ≤40 kg/m^2.
12. Absence of impaired hepatic function. Impaired hepatic function is characterized by a previous known diagnosis of chronic liver disease, and/or 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.
13. Calculated creatinine clearance ≥60 mL/minute (Cockcroft-Gault formula).
14. Fasting triglycerides ≤600 mg/dL.
15. Except as noted in criteria 12-14 above, clinical laboratory values must be within normal limits, or deemed not clinically significant by the Investigator.
16. 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.
17. 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.
18. Has not participated in an interventional study for at least 30 days or has not taken 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.
19. Ability to understand the requirements of the study, abide by the study restrictions, as well as concomitant medications exclusions, and agree to return for the required assessments.
20. 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.

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 criteria will NOT be allowed.

7.2. Subject Exclusion Criteria

Subjects who meet ANY of the following criteria will be excluded from the study.

1. Current diagnosis of major psychiatric disorder (including schizophrenia and/or bipolar disorder), including subjects who have required an antipsychotic (e.g., aripiprazole, asenapine, cariprazine, clozapine, lurasidone, olanzapine, quetiapine, risperidone, ziprasidone) or mood stabilizer (e.g., lithium, carbamazepine, lamotrigine valproate) for a psychiatric condition in the past year, or subjects who have had a major depressive episode (MDE) in the past 6 months. Subjects with major depressive disorder (MDD), generalized anxiety disorder (GAD) or panic disorder who have been on stable medication for the past 3 months (and are expected to remain stable for the duration of the study) and whose condition is currently well-controlled may be included.
2. Pain that cannot be clearly differentiated from, or could interfere with, the assessment of peripheral diabetic neuropathy, as measured by the Masquerading Disorders Tool at Visit 1.
3. Neurologic disorders unrelated to diabetic neuropathy (e.g., phantom limb from amputation), skin condition in the area of neuropathy that could alter sensation (e.g., plantar ulcer), or other painful conditions (e.g., arthritis) that, in the judgment of the investigator, could interfere with reporting of pain due to diabetic neuropathy.
4. History of hypoglycemia that disturbed consciousness, or ketoacidosis requiring hospitalization within past 3 months.
5. History of severe renal impairment defined by renal dialysis or peritoneal dialysis, or has undergone renal transplant.
6. 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 or 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.
7. Pulse rate <45 bpm or >90 bpm.
8. 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.
9. Positive serology test result for HIV or current hepatitis B or C infection, or other ongoing infectious disease that the investigator considers clinically significant.
10. 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 period should be completed during screening, with last dose being at least two (2) weeks prior to randomization (See Section 15.1 of the protocol for Disallowed Analgesic and Other Medications).

11. Current or recent (within 12 months of screening) history of a substance use disorder including cannabinoid use disorder.

12.

a. Visit 1: 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. Visit 2: Positive urine drug screen for benzodiazepines inconsistent with protocol specified allowed prescriptions, psychoactive cannabinoids (e.g., marijuana, THC) inconsistent with subject reported use, PCP, opioids, cocaine, or amphetamines at Visit 2.

13. Sensitivity to, allergy to, or concomitant use of *N*-methyl-D-aspartate receptor ligands including ketamine, esketamine, amantadine, dextromethorphan, memantine, methadone, dextropropoxyphene, lamotrigine, and/or ketobemidone.

14. Use of NMDAR-binding drugs (e.g., ketamine, esketamine, amantadine, dextromethorphan, memantine, methadone, dextropropoxyphene, lamotrigine, and/or ketobemidone) within 30 days prior to dosing or during the study. Use of high concentration capsaicin patch within 3 months prior to screening; use of lidocaine patch within 1 month prior to screening.

15. Sensitivity to or intolerance to acetaminophen or associated formulation components.

16. Hypersensitivity or intolerance to multiple medications, in the opinion of the investigator.

17. Amputations of lower extremities (toe(s) amputation is allowed).

18. 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.

19. Planned surgery during study participation.

20. Active malignancy or a history of malignancy (except for treated non-melanoma in-situ skin cancer) within 5 years of screening.

21. 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.

22. 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. Presence of an exclusionary masquerading disorder in the Masquerading Disorders Tool (MDT) assessment.

23. 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 diabetes) that may interfere with study participation, as assessed the investigator.

24. Previous randomization in current or previous NYX-2925 clinical trials.
25. Subject has filed for a disability claim or has any pending worker's compensation litigation.
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.

Waivers to the exclusion criteria will NOT be allowed.

7.3. Screen Failures

Subjects who sign and date the informed consent forms, but who fail to meet the inclusion and exclusion criteria, will be considered screen failures. Reason(s) for screen failure must be documented by the Investigator. Screen failures may be rescreened, at the investigator's discretion. Subjects who are randomization ineligible may not be rescreened. Rescreened subjects will be assigned new subject numbers.

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 the 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. 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. Accurate 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 capsule of study drug once daily by mouth. The first dose of study drug will be taken in the clinic during Visit 2 (Week 0). Subjects will be instructed to take study drug once daily throughout the study.

Subject will be randomized to doses of NYX-2925 50 mg or placebo by mouth, once daily.

Subjects will also be dispensed one (1) bottle of acetaminophen to be used as rescue medication at visit 1. Rescue medication will be dispense/re-dispensed at the visits identified in Table 3.

Rescue medication will consist of 500 mg tablets of acetaminophen. Subjects will be instructed to take one to two 500 mg tablets every 6 hours as needed up to 4 tablets total for DPN related pain, not to exceed 2 g/day. Rescue medication will be provided by the Sponsor. Rescue medication use should be reported daily via the study issued- handheld device.

8.2. Study Drug and Rescue Medication 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 NYX-2925 per capsule. Matching placebo capsules will also be provided.

[redacted]

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

Acetaminophen rescue medication will be provided in bottles containing 500 mg tablets of acetaminophen. The labels will include "Acetaminophen 500 mg", bottle number, protocol number, a space for subject number and Sponsor name. Subjects will be instructed to take no more than 2 g/daily (one to two 500 mg tablets every 6 hours and up to 4 tablets total) as needed for DPN related pain. Subjects will be dispensed 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, and there will be no study drug preparation done at the investigative site. The Investigator may delegate study drug management to site personnel who will dispense kits of study drug for subject administration according to the IRT system. The IRT system will be 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 directions regarding excursions.

8.5. Accountability

The Investigator or designee at the investigative site will conduct study drug accountability for study drug and rescue medication. 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 representative will inspect study drug and rescue medication accountability records. Site personnel will conduct subject-level accountability, account for and document used containers/unused study drug and rescue medication, and the site will retain containers of returned study drug and rescue medication in the investigative site's limited access storage facility.

Upon completion or termination of the study and after Sponsor accountability is completed, all used and unused study drug and containers will be returned to the depot as instructed by Sponsor 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 medications, taken for neuropathic pain associated with diabetic peripheral neuropathy, with the exception of acetaminophen (rescue medication). Rescue medication may be taken for DPN related pain only. Subjects may continue their antidiabetic medications. Adjustment of diabetic medications may be made, as necessary, for the best management of a subject's underlying condition by the investigator or the subject's healthcare provider. Stable doses of the benzodiazepines alprazolam or 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. Intermittent 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 DPN as described below, systemic corticosteroids, opioid or

narcotic analgesics, muscle relaxants, tramadol, injected or topical lidocaine, injected or topical capsaicin, norepinephrine reuptake inhibitors (NRIs), serotonin-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 or 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 DPN 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 2 g/day (one to two 500 mg tablets every 6 hours as needed up to 4 tablets total) for DPN related pain. Rescue medication will be provided by the Sponsor.

For pain unrelated to DPN, 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 DPN, the medication should be recorded as a concomitant medication and the adverse event must be recorded in the eCRF.

Medications used 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. Masquerading Disorders Tool

The Masquerading Disorders Tool (Analgesic Solutions, Wayland, MA) is a screening instrument to help identify subjects with disorders that masquerade as painful diabetic peripheral neuropathy, such as Morton's neuroma, peripheral vascular disease, Achilles tendonitis, arthritis, and tarsal tunnel syndrome. The screening instrument consists of symptom screening questions and an in-clinic history and examination to target the nature and etiology of the subject's peripheral pain. The results of this assessment tool are provisional, with the final decision based on the clinical judgment of the Investigator.

9.1.3. Michigan Neuropathy Screening Instrument

The Michigan Neuropathy Screening Instrument (MNSI) is a 15-item, self-administered questionnaire and a 5-item clinician-administered lower extremity examination that includes inspection of vibratory sensation and ankle reflexes. It can be used to assess distal symmetrical peripheral neuropathy in diabetes [Herman 2012].

9.1.3.1. MNSI Modified Scoring

On the self-administered questionnaire, 'Yes' responses to questions 1–6, 8–12, 14–15 are each counted as one point, and 'No' responses to questions 7 and 13 each count as one point. On the lower extremity examination, responses for the left and right feet were combined for the following measures of the examination: ulceration, ankle reflex, vibration perception at great toe, and monofilament. Ulceration was scored as one point if present in either lower extremity. Ankle reflex was scored as 0.5 point if present/reinforcement in one lower extremity and one point if absent in one or both lower extremities. Vibration was scored as 0.5 point if decreased in one lower extremity and one point if absent in one or both lower extremities. Monofilament was scored as 0.5 point if reduced in one lower extremity and one point if absent in one or both lower extremities. (Appearance from the clinical examination is not scored.)

The self-administered questionnaire has a maximum score of 15 points, and the clinical examination has a maximum score of 4 points, resulting in a total maximum possible score on the MNSI of 19 points [Herman 2012].

9.2. Efficacy Assessments

9.2.1. Numeric Rating Scale of Pain Intensity

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 that is anchored by terms defining pain levels, where

0 represents no pain and 10 represents worst pain imaginable.

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

9.2.2. Patient Global Impression of Change

The PGI-C is a 7-point scale that 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 [Guy W 1976].

9.2.3. Norfolk Quality of Life Questionnaire – Diabetic Neuropathy (QOL-DN)

The Norfolk QOL-DN is a 47-item, subject-reported questionnaire designed to measure the relationship between symptomatic diabetic neuropathy and quality of life from the perspective of the patient. It is composed of 2 parts: questions related to symptoms experienced by the patient and questions related to the impact of the patient's neuropathy on activities of daily life. A factor analysis performed on the Norfolk QOL-DN separated the questions into 5 domains: activities of daily living, symptoms, small fiber neuropathy, large fiber neuropathy, and autonomic neuropathy. The QOL-DN is sensitive to the different features of diabetic neuropathy including small fiber, large fiber, and autonomic nerve function [Vinik 2005].

9.2.4. Daily Sleep Interference Scale

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].

9.2.5. Brief Pain Inventory for Diabetic Peripheral Neuropathy

The BPI-DPN is a patient-completed numeric rating scale that assesses the severity of pain (Severity scale), its impact on daily functioning (Interference scale), and other aspects of pain (e.g., location of pain, relief from medications). A modified version of the BPI-DPN, including the 4-item pain Severity scale (Worst Pain, Least Pain, Average Pain, and Pain Now) and the 7-item pain Interference scale (General Activity, Mood, Walking Ability, Normal Work, Relations With Others, Sleep, Enjoyment of Life) has been validated in patients with painful diabetic peripheral neuropathy) and distinguishes between pain due to diabetic peripheral neuropathy and pain due to other causes. Each item uses a 0 to 10 numeric rating scale anchored at 0 for “no pain” and 10 for “pain as bad as you can imagine” for Severity, and “does not interfere” to “completely interferes” for Interference. The 4 Severity items and the 7 Interference items can also each be averaged to form 2 composite scores, the Pain Severity Index and the Pain Interference Index [Zelman 2005].

9.2.6. 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 “normal”, two (2) corresponds to “mild”, three (3) corresponds to “moderate” and four (4) corresponds to “severe” [Guy W 1976].

9.2.7. Pain Catastrophizing Scale (PCS)

The PCS is a 13-item instrument that assesses the state of mind of patients in pain through a comprehensive evaluation instrument that encompasses the different perspectives on catastrophizing. Factor analyses of the PCS have shown that catastrophizing can be viewed as a multidimensional construct comprising elements of rumination (“I can’t stop thinking about how much it hurts”), magnification (“I worry that something serious may happen”), and helplessness (“There is nothing I can do to reduce the intensity of the pain”). The PCS instructions ask participants to reflect on past painful experiences, and to indicate the degree to which they experienced each of 13 thoughts or feelings when experiencing pain, on 5-point scales with the end points (0) not at all and (4) all the time. The PCS total score is computed by summing responses to all 13 items. PCS total scores range from 0 – 52. The PCS subscales are computed by summing the responses to rumination, magnification, and helplessness items [Sullivan 1995].

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 sitting or lying supine for at least five (5) minutes 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, and dermatologic systems; and extremities.

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

A brief physical examination will be completed at Week 12/Early Termination.

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 ECGs with a minimum of a two minute interval between each ECG will be collected at screening, and a standard 10-second ECG will be collected at baseline, week 8 and week 12/ET after at least five (5) minutes of supine rest and prior to blood sample collection, if possible. The device will be a Spaulding (Spaulding Medical, West Bend, WI) electrocardiogram (ECG) device that acquires a 12-lead ECG. The ECG data will be submitted to the designated ECG laboratory cardiologists for measurements and diagnoses.

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

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

9.3.5. Clinical Laboratory Assessments

Blood samples for hematology and chemistry will be obtained after an 8-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. Hemoglobin A1c will be assessed at Visit 1 and Visit 6/Early Termination.

Chemistry assessments will include glucose, calcium, electrolytes (sodium, potassium, bicarbonate, chloride), phosphorus, blood urea nitrogen (BUN), creatinine, creatinine clearance, 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). Triglycerides and a thyroid panel (TSH, T_3, T_4, and free T_4) will also be measured 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 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.

If the screening test for HIV antibody is positive, confirmatory test may be performed.

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

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

9.3.6. Sheehan-Suicidality Tracking Scale

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 studies, 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, 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 event will be recorded as an adverse event.

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 (e.g., a clinically significant change detected on clinical chemistry, hematology, or urinalysis results) that is independent from the underlying medical condition and that 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 the 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 "pre-existing" 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.

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 discontinuation
- 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. Serious adverse events are reported to the Sponsor or designee using the provided form 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 1 of the outcomes listed previously (e.g., 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 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 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 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 (e.g., additional diagnostic 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.

9.5. 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 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 of the prior research study, violation of the washout period between studies, incorrect age for the NYX-2925-2008 study, or previous randomization into a clinical trial of NYX-2925. Employees, contractors, or volunteers of the study site, 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 collect 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 diabetic peripheral neuropathy will then be required to discontinue their analgesia and "wash out" 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 painful diabetic neuropathy 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.

Prior to recording their first pain score in the handheld device, each subject will undergo educational training on Accurate Pain Reporting (APR®) and Placebo Response Reduction (PRR®) via an electronic learning management system, aLearn® [Analgesic Solutions, Wayland, MA].

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, including history of Type 2 diabetes and history of painful DPN
- Prior (within last 30 days) and concomitant medications
- S-STS
- Adverse events
- Confirmation of diabetic peripheral neuropathy by the following assessments:
  - MNSI
  - MDT
- PGI-S
- Height and body weight
- Vital signs (blood pressure and pulse after sitting or lying supine for at least five (5) minutes)
- Complete physical examination, including comprehensive neurological examination
- Triplicate ECG after at least five (5) minutes in supine position with a minimum of a two minute interval between ECGs
- Fasting (8 hours) blood samples for hematology, serum chemistry, triglycerides, HbA1c, and a thyroid panel (TSH, T3, T4 and free T4)
- Blood samples for screening for HIV, hepatitis B and hepatitis C
- Urine sample for urinalysis
- Urine pregnancy test for females of childbearing potential
- Urine drug screen

Eligible subjects who meet all the inclusion criteria and none of the 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 neuropathic pain associated with diabetic peripheral neuropathy, 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 4 weeks (see Section 15.1 of the protocol for Disallowed Analgesic and Other Medications). Subjects already 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, worst pain intensity, average pain upon walking, and rescue medication use 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 2 g/day (one to two 500 mg tablets every 6 hours as needed up to 4 tablets total) for DPN related pain.

10.2. Baseline Visit: Week 0/Visit 2

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

- Concomitant medication use
- PGI-S
- S-STS
- Adverse events
- Vital signs (blood pressure and pulse after sitting or lying supine for at least 5 minutes)
- ECG after at least five (5) minutes in supine position
- Fasting (8 hours) blood samples for hematology and serum chemistry
- Urine sample for urinalysis
- Urine pregnancy test for females of childbearing potential
- Urine drug screen
- 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 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 IRT system will undergo the following procedures and assessments:

- BPI-DPN
- QOL-DN
- PCS

- 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 past 24 hours in the handheld device upon awakening in morning.
- Re-dispensing/dispensing of rescue medication – Subjects will be reminded not to exceed 2 g/day (one to two 500 mg tablets every 6 hours as needed up to 4 tablets total) for DPN related pain.
- Subjects will be reminded of 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 at each site-based study visit, with the exception of the final visit. An ongoing blinded data review (e.g., if pain score variability is increased on a subject or site level) will be conducted to monitor these metrics [Analgesic Solutions, Wayland, MA]. On each day until returning to the study site at Week 4/Visit 4, subjects will record the following on the handheld device:
  - At bedtime: average pain intensity, worst pain intensity, average pain upon walking, and rescue medication use during the past 24 hours.
  - Upon waking: DSIS, confirm they have taken study drug.
- 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
- MADDERS
- Rescue medication appropriate use assessment by review of daily use entries in the handheld diary as well as by subject interview
- Study drug use and assessment of compliance by review of daily use entries in the handheld diary, as well as by subject interview
- Study drug use and assessment of compliance by review of daily use entries in the handheld diary and by subject interview Compliance with entry into daily diary of pain intensity, rescue medication use, and study drug administration
- Subjects will be instructed to take one capsule of study drug by mouth once daily.

- Subjects will be reminded not to exceed 2 g/day (one to two 500 mg tablets every 6 hours as needed up to 4 tablets total) for DPN related pain.
- Subjects will be reminded of how to record their pain on the device and will also be reminded about appropriate expectations for their participation in a clinical study. Review of these educational materials will be repeated for all subjects within the aLearn® portal at each site-based study visit, with the exception of the final visit. An ongoing blinded data review (e.g., if pain score variability is increased on a subject or site level) will be conducted to monitor these metrics [Analgesic Solutions, Wayland, MA]. On each of day until returning to the study site at Week 4 (Visit 4), subjects will record the following on the handheld device:
  - At bedtime: average pain intensity, worst pain intensity, average pain upon walking, and rescue medication use during the past 24 hours
  - Upon waking: DSIS and confirm they have taken study drug
- 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

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

- Concomitant medication use
- S-STS
- Adverse events
- MADDERS
- Vital signs (blood pressure and pulse after sitting or lying supine for at least five (5) minutes)
- Fasting (8 hours) blood samples for serum chemistry and hematology
- Urine sample for urinalysis
- Urine pregnancy test, if clinically indicated for females of childbearing potential
- Urine drug screen
- BPI-DPN
- PGI-C
- QOL-DN
- Rescue medication return and 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, rescue medication use, and study drug administration

- 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 2 g/day (one to two 500 mg tablets every 6 hours as needed up to 4 tablets total) for DPN related pain
- Subjects will be reminded of 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 at each site-based visit, at each site-based visit, with the exception of the final visit. An ongoing blinded data review (e.g., if pain score variability is increased on a subject or site level) will be conducted to monitor these metrics [Analgesic Solutions, Wayland, MA]. On each of 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, worst pain intensity, average pain upon walking, and rescue medication use during the past 24 hours
  - Upon waking: DSIS and confirm they have taken their study drug Subjects will be instructed to return to the study site at Week 8 (Visit 5).

10.3.3. Week 8/Visit 5

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

- Concomitant medication use
- S-STS
- Adverse events
- MADDERS
- Vital signs (blood pressure and pulse after sitting or lying supine for at least five (5) minutes)
- ECG after at least five (5) minutes in supine position
- Fasting (8 hours) blood samples for serum chemistry and hematology
- Urine sample for urinalysis
- Urine pregnancy test, if clinically indicated for females of childbearing potential
- Urine drug screen
- Compliance with entry into daily diary of pain intensity, rescue medication use, and study drug administration
- Rescue medication return and 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

- 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 2 g/day (one to two 500 mg tablets every 6 hours as needed up to 4 tablets total) for DPN related pain
- Subjects will be reminded of how to record their pain on the device and will also be reminded about appropriate expectations for their participation in a clinical study. Review of these educational materials will be repeated for all subjects at each site-based visit, with the exception of the final visit. An ongoing blinded data review (e.g., if pain score variability is increased on a subject or site level) will be conducted to monitor these metrics [Analgesic Solutions, Wayland, MA]. On each of day until returning to the study site at Week 12 (Visit 6), subjects will record the following on the handheld device:
  - At bedtime: average pain intensity, worst pain intensity, average pain upon walking, and rescue medication use during the past 24 hours
  - Upon waking: DSIS and confirm they have taken their study drug Subjects will be instructed to return to the study site at Week 12 (Visit 6).

10.3.4. Week 12/Visit 6/Early Termination

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
- MADDERS
- Body weight
- Vital signs (blood pressure and pulse after sitting or lying supine for at least five (5) minutes)
- Brief physical examination
- ECG after at least five (5) minutes in supine position
- Fasting (8 hours) blood samples for serum chemistry and hematology, including HbA1c
- Urine sample for urinalysis
- Urine pregnancy test for females of childbearing potential
- Urine drug screen
- BPI-DPN
- PGI-C
- QOL-DN
- PCS

- Compliance with entry into daily diary of pain intensity, rescue medication use, and study drug administration
- Rescue medication return and 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
- Study-issued handheld device and other equipment/documents return
- 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 newly reported 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 measures (ALT, AST, ALP, and TBL) should conducted to confirm the abnormalities and to determine if they are increasing or decreasing.

12. STATISTICS

12.1. Sample Size

The planned sample size is a total of 204 randomized subjects. This will provide approximately 80% power using 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 seven (7) days is within the protocol-defined algorithm and whose compliance with daily diary completion is adequate will be eligible for randomization. The absolute pain scores and variability among scores, as well as the actual percentage required for diary compliance, will be masked to investigators and subjects. Subject eligibility for randomization into the study based on these variables will be communicated to the investigator via the IRT system. The IRT system will notify the site if the subject is "Eligible" or "Not eligible." No other information will be provided.

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 percentage 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 non-missing 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
- Placebo

The following treatment group comparisons will be performed for efficacy:

- NYX-2925 50 mg versus placebo

12.6. Analyses of Efficacy

12.6.1. Primary Efficacy Endpoint

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

12.6.1.1. 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 weekly mean of the daily average pain intensity NRS score from the handheld device will be averaged for baseline after randomization. Change from baseline will be assessed for treatment group differences 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.

12.6.1.2. 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 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 (increase) 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.

12.6.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints will be tested:

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

12.6.3. Other Efficacy Analyses

[redacted]

12.6.4. 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) in a hierarchical manner to preserve the overall Type I error rate. There will be no adjustment for multiple comparisons for other efficacy endpoints.

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 percentage of subjects experiencing TEAEs by system organ class and preferred term. If a subject has more than 1 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 1 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:

- 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 change 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 diagnostic reports, medical histories, hospital records, and study 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. Electronic Case Report Forms (eCRF)

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 designated Sub-investigator 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 documents, and all relevant supporting data must be submitted to the Institutional Review Board (IRB) for approval. IRB approval of the protocol, informed consent documents, and any subject-facing materials 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. Subjects will also be asked to provide 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 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 must be reconsented with the IRB-approved revised ICF 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, 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' identity 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 2 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 2 years after the investigation has been discontinued and the FDA has been notified. Per ICH guidelines, documents should be retained until ≥2 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 ≥2 years have elapsed since the formal discontinuation of clinical development of the study drug. Aptinyx will notify the Investigator in writing when records and documents no longer need to be retained. No study records should be destroyed without prior written authorization.

13.15. Publication Policy

The publication policy is outlined in the Clinical Trial Agreement.

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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) [e.g., duloxetine (Cymbalta®), milnacipran (Savella), venlafaxine (Effexor®), desvenlafaxine (Pristiq®), levomilnacipran (Fetzima®)],
- Anti-epileptics, e.g., 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 DPN
- Topical therapies: topical capsaicin; topical/local anesthetic lidocaine

*Any non-pharmacologic therapies or interventions for treatment of pain that are not on this list must be discussed with the Medical Monitor prior to screening (e.g., 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.