NCT03249103

NYX-2925-2002

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

Protocol

March 7, 2018

STUDY DRUG: NYX-2925

CLINICAL PROTOCOL: NYX-2925-2002

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

Amendment #3

Sponsor: Aptinyx Inc.

[redacted]

IND Number: 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 Practices (GCPs), including the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) 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 ICH E6 Guideline for Good Clinical Practice, and all applicable laws and regulations including, but not limited to those related to data privacy and clinical trial disclosure.

[redacted]

[redacted]

Date

[redacted]

[redacted]

Date

[redacted]

[redacted]

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
Senior Director, Clinical Research 24-Hour Emergency Contact	[redacted]	[redacted]
Clinical Manager, Clinical Research Primary Contact	[redacted]	[redacted]
Medical Monitor Physician	[redacted]	[redacted]
Serious Adverse Event Reporting Information		
Email: [redacted]	Fax: [redacted]	

1. SYNOPSIS

Name of sponsor/company: Aptinyx Inc.	
Name of investigational product: NYX-2925	
Name of active ingredient: (2S, 3R)-3-hydroxy-2-((R)-5-isobutyryl-1-oxo-2,5-diazaspiro[3.4]octan-2-yl)butanamide	
Title of study: A Phase 2, Single-Blind, Exploratory, Placebo-controlled, Pilot Study to Assess the Efficacy and Safety of Daily Oral NYX-2925 in Subjects with Fibromyalgia	
Study Sites: Approximately 2 sites	
Investigators: Multicenter	
IND Number: 129731	
Studied period (years): Estimated date first subject enrolled (randomized): Approximately June 2017 Estimated date last subject completed: approximately November 2018	**Phase of development:** 2

Objectives

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

[redacted]

- **Secondary objectives:** To evaluate the safety of NYX-2925 in subjects with fibromyalgia.

Exploratory analyses: [redacted]

[redacted]

Methodology:

Study Design

The study will include up to a 30-day screening period, to confirm the diagnosis, assess eligibility, and complete the baseline magnetic resonance imaging (MRI). This is a single-blind, exploratory, placebo-controlled, pilot study in which eligible subjects will receive 2 weeks of daily oral placebo, 2 weeks of NYX-2925 20 mg PO daily (low dose), 2 weeks of NYX-2925 200 mg PO daily (high dose), followed by a 1 week follow-up period. An MRI will be conducted during the screening period, during the last week of the placebo period, during the last week of the NYX-2925 20 mg administration period, and during the last week of the NYX-2925 200 mg administration period. Study visits will occur during screening, then at Day 1 and weeks 1, 2, 3, 4, 5, 6, and 7. An optional MRI will be completed at the end of the follow-up period for consenting subjects. Study participants and study staff responsible for interpreting MRI results will be blinded to the study drug administration.

Study drug (NYX-2925 or matching placebo) will be dispensed to subjects for self-administration.

Subjects will record daily pain scores for the entire duration of the study. Other exploratory scales will be completed during screening, after placebo, after NYX-2925 20 mg administration, after NYX-2925 200 mg administration, and, after the follow-up period.

Adverse events (AEs), vital signs, electrocardiograms, physical examinations, Columbia Suicide Severity Rating Scales, and clinical laboratory samples will be collected throughout the study.

Number of subjects (planned):

24 enrolled subjects

Diagnosis and main criteria for inclusion:

Inclusion Criteria

[redacted]

2. Subject meets the 2010 American College of Rheumatology criteria for fibromyalgia.
3. Self-reported clinical pain ≥ 4 on the Numeric Pain Rating Scale (NPRS) at screening and baseline, and consistent pain score collection during screening.
4. Subject receives and agrees to remain on their stable fibromyalgia treatment plan [redacted]
5. Subject agrees to use only non-steroidal anti-inflammatory (NSAID) or acetaminophen treatment as needed for breakthrough pain, and/or protocol specified medications for sleep (if needed).
6. Right handed.
7. [redacted]
8. Female subjects of child bearing potential with a negative serum pregnancy test prior to entry into the study and who are practicing an adequate method of birth control [redacted]
9. Ability to understand the requirements of the study, provide written informed consent, abide by the study restrictions, and agree to return for the required assessments.

Exclusion Criteria

1. Current or expected use of opioid or narcotic analgesics [redacted]
2. [redacted]
3. Pain due to concurrent autoimmune or inflammatory disease [redacted]
4. Untreated endocrine disorder that may confound fibromyalgia assessments.
5. Psychiatric or cognitive disorder [redacted]
6. Clinically significant alcohol or other substance abuse within the last 2 years, in the opinion of the investigator.
7. Positive screen for medically inappropriate or illegal use of drugs of abuse [redacted]
8. Current treatment with N-methyl-D-aspartate receptor (NMDAR) ligands including ketamine, amantadine, dextromethorphan, memantine, methadone, dextropropoxyphene, or ketobemidone.
9. History of allergy, sensitivity, or intolerance to NMDAR ligands including ketamine, amantadine, dextromethorphan, memantine, methadone, dextropropoxyphene, or ketobemidone.
10. Women who are pregnant, breast feeding, or planning to become pregnant or donate ova during the course of the study. and for 28 days after the final administration of investigational product
11. Any impairment, activity or situation that in the judgment of the investigator would prevent satisfactory completion of the study protocol. This includes unreliable or inconsistent pain scores, or an inability to tolerate the MRI procedure during screening.
12. Huntington's, Parkinson's, Alzheimer's, Multiple Sclerosis, or a history of seizures, epilepsy, or strokes.
13. Contraindications to fMRI procedures. [redacted]
14. [redacted]
15. Abnormal laboratory results, medical history, or concurrent conditions that, in the opinion of the investigator or sponsor designated medical monitor, would preclude safe study participation, or interfere with study procedures/assessments.
16. [redacted]
17. Subjects with history of severe renal impairment [redacted]
18. Known history of significant cardiovascular condition [redacted]

19. Current evidence of dysplasia or history of malignancy [redacted]
20. Human immunodeficiency virus (HIV) infection, hepatitis, or other ongoing infectious disease that the investigator considers clinically significant.
21. History of severe renal or hepatic impairment, in the opinion of the investigator or the sponsor designated medical monitor.
22. History of photosensitive migraine or migraine with aura, which in the opinion of the investigator, would be contraindicated in MRI procedures.
23. History of lower limb vascular surgery or current lower limb vascular dysfunction that would interfere with MRI procedures, in the opinion of the investigator.
24. Received an investigational drug or device within 30 days (or 5 half-lives, whichever is longer) of dosing.
25. Previous treatment with NYX-2925.
26. [redacted]

Investigational product, dosage and mode of administration:

NYX-2925, 10 and 100 mg oral capsules

NYX-2925 low dose: 20 mg (two 10 mg capsules) PO QD for 2 weeks

NYX-2925 high dose: 200 mg (two 100 mg capsules) PO QD for 2 weeks

Duration of treatment/study (up to approximately 11 weeks):

- Screening period – up to 30 days
- Placebo once daily for 2 weeks
- NYX-2925 for 4 weeks
- Follow-up period for 1 week

Reference therapy, dosage and mode of administration:

Placebo, oral capsule(s)

2 placebo capsules PO QD for 2 weeks

Criteria for evaluation:

Efficacy:

[redacted]

Safety:

- Adverse events
- Vital sign measurements
- Clinical laboratory test results
- Electrocardiogram results
- Physical examination findings
- Columbia-Suicide Severity Rating Scale (C-SSRS)

Exploratory Analyses:

[redacted]

- Quantitative Sensory Testing [redacted]

Statistical methods:

- Sample size rationale: Not applicable, this study is not statistically powered
- Interim analysis plan: None

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

TABLE OF CONTENTS

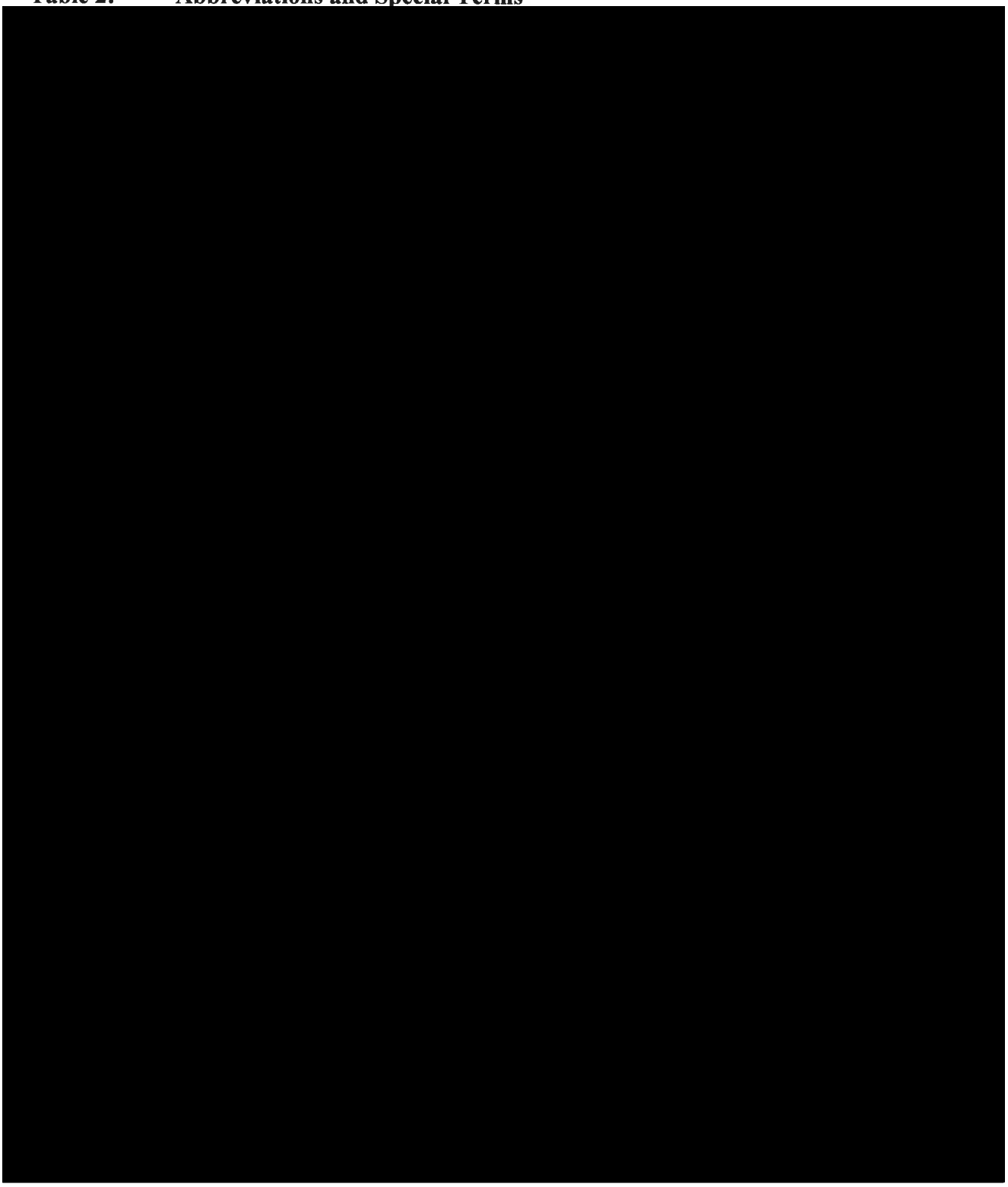
LIST OF TABLES

LIST OF FIGURES

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



[redacted]

4. INTRODUCTION

NYX-2925 is a novel small molecule being developed for the treatment of neuropathic pain and fibromyalgia. [redacted]

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

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

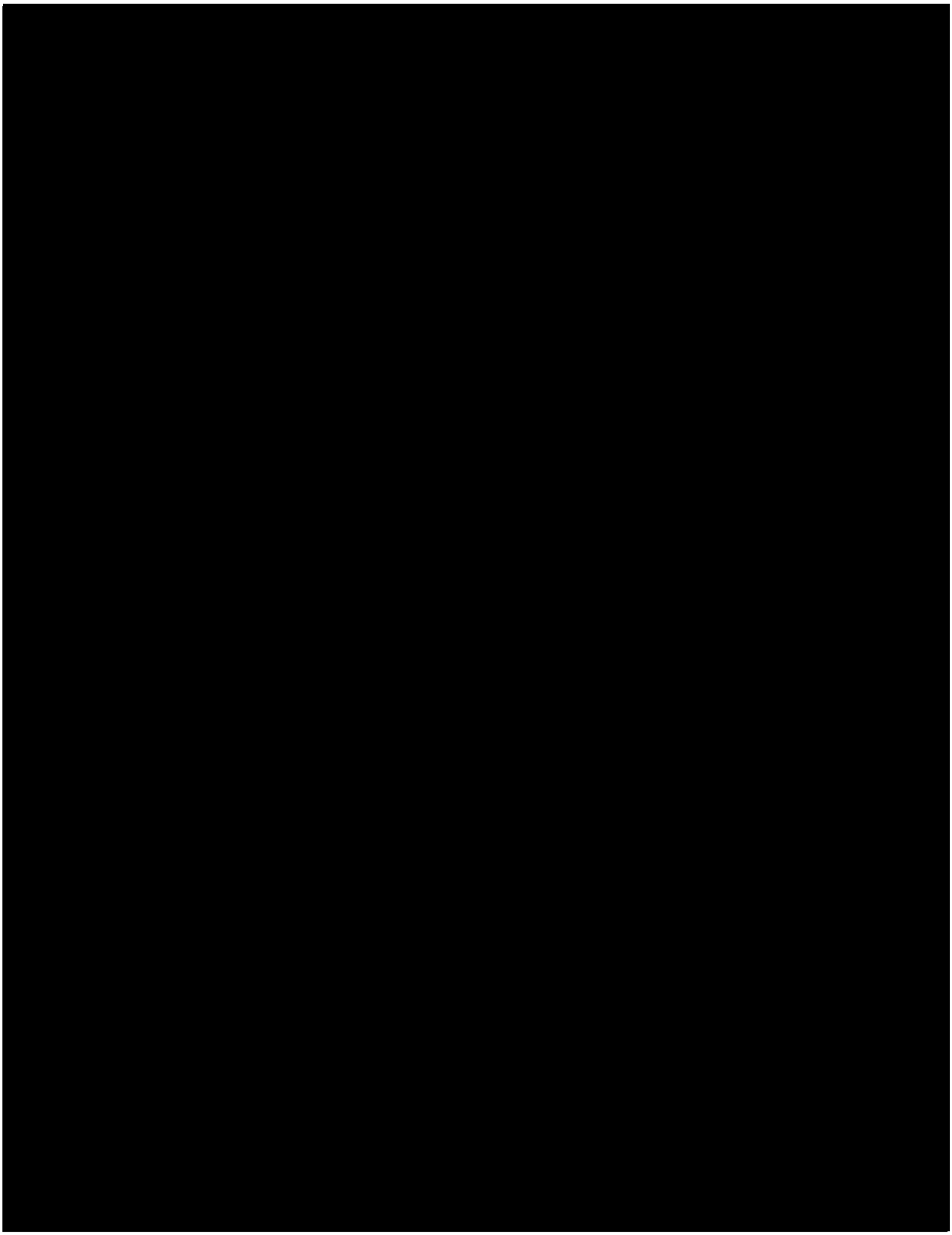
Individuals suffering from fibromyalgia presently have limited treatment options available. Current treatment options include pregabalin, a calcium channel alpha-2-delta subunit ligand, and 2 norepinephrine and serotonin reuptake inhibitors, duloxetine and milnacipran. These therapies have shown some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

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

As in fibromyalgia, the central nervous system (CNS) 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 (Gilron 2015). CNS modulation of the experience of pain is common, regardless of the specific precipitating factors or initial location of the pain.

[redacted]



5. STUDY OBJECTIVES AND ENDPOINTS

5.1. Primary Objective

The primary objective is to determine whether daily dosing with an NYX-2925 20 or 200 mg regimen changes markers of central pain processing in subjects with fibromyalgia by evaluating

[redacted]

5.2. Secondary Objectives

The secondary objective is to evaluate the safety of NYX-2925 in subjects with fibromyalgia.

5.3. Study Endpoints

5.3.1. Efficacy Endpoints

Functional magnetic resonance image will be evaluated for changes to central pain processing markers to examine if NYX-2925:

1. Attenuates pain-evoked and aversive visual stimulus-evoked brain activation versus placebo;
2. Reduces resting state functional connectivity between the insula and the Default Mode Network versus placebo;
3. Reduces combined glutamate plus glutamine (Glx) levels within pro-nociceptive brain regions, such as the insula and anterior cingulate cortex versus placebo.

5.3.2. Safety Endpoints

The safety endpoints will include adverse events (AEs), C-SSRS, vital sign changes, physical examination findings, clinically important electrocardiogram changes, and clinically important laboratory result changes.

[redacted]

6. INVESTIGATIONAL PLAN

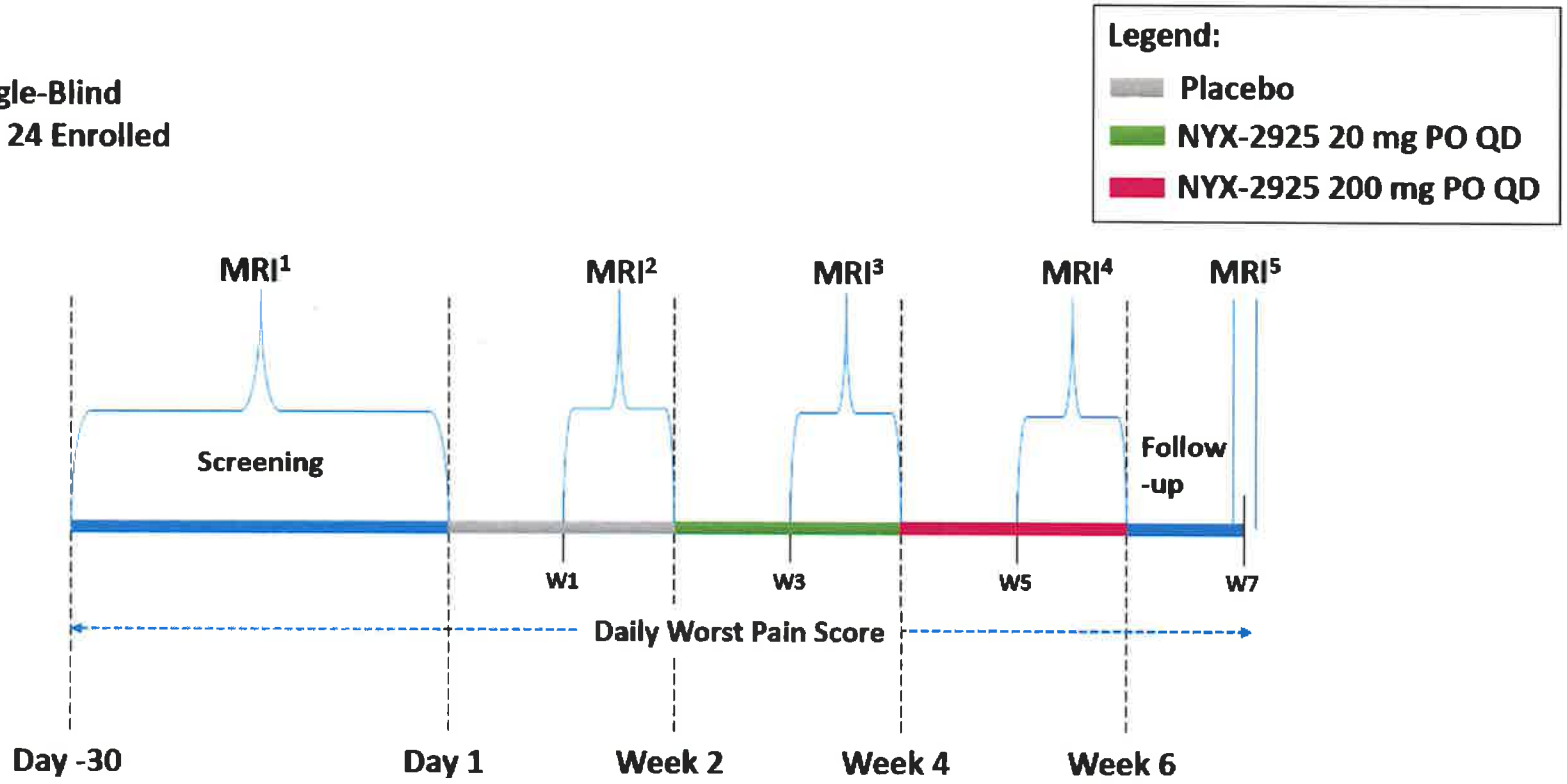
6.1. Overall Study Design and Plan: Description

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

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

Eligible subjects will receive MRIs during the screening period, during the placebo period, during the NYX-2925 20 mg PO QD period, and during the NYX-2925 200 mg PO QD period. Safety assessments will be conducted and adverse events will be collected during the study. Daily pain scores and other fibromyalgia scales will be collected for exploratory analysis. During the follow-up period, an optional MRI will be completed for consenting subjects in order to evaluate duration of effect.

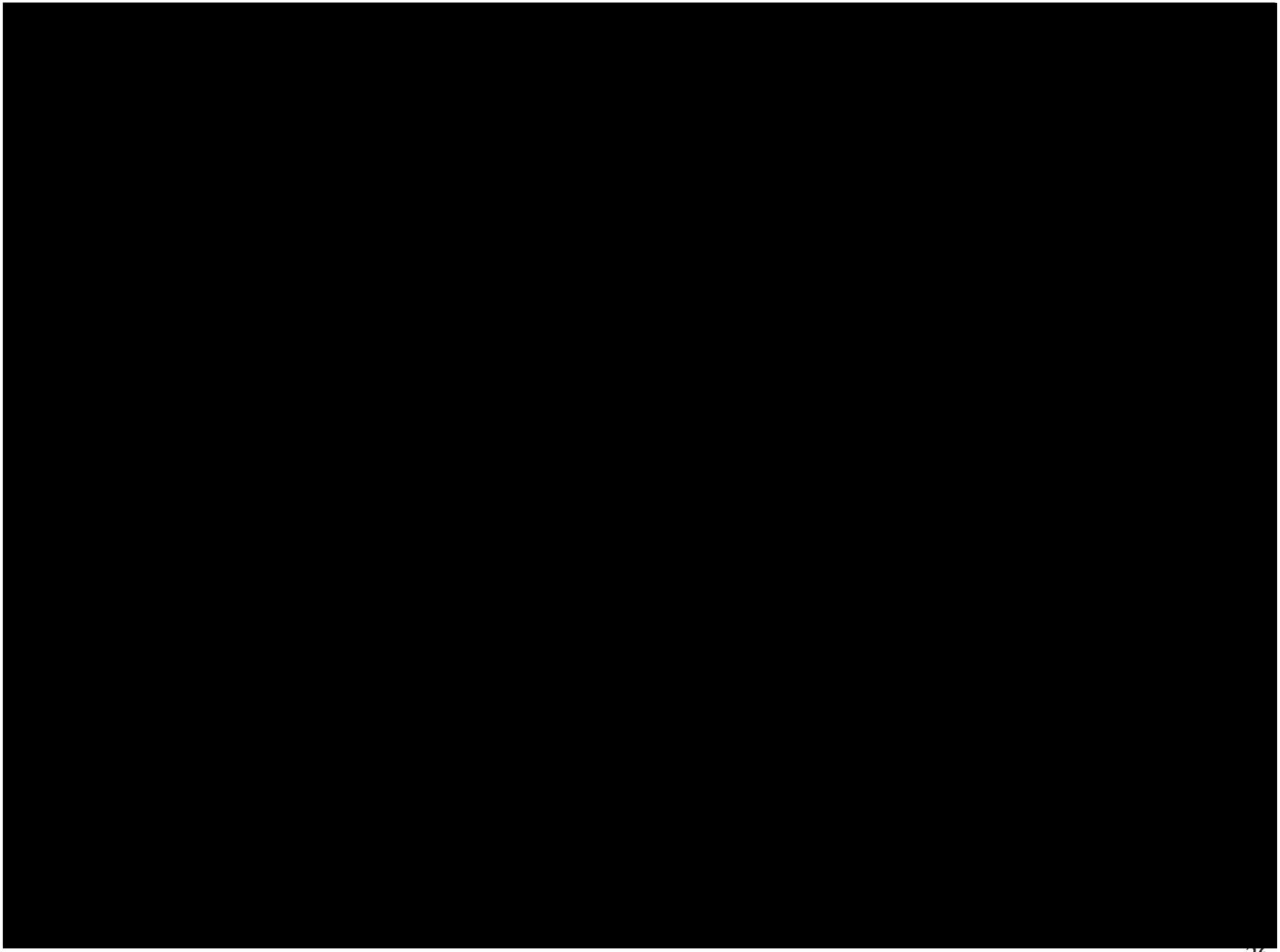
Figure 1: Study Design



MRI[1] - conducted during screening period
MRI[2] - conducted between Weeks 1 and 2 of placebo administration
MRI[3] - conducted between Weeks 3 and 4 of NYX-2925 20 mg PO QD
MRI[4] - conducted between Weeks 5 and 6 of NYX-2925 200 mg PO QD
MRI[5] – (Optional) conducted at Week 7 ± 2 Days

Table 3: Schedule of Assessments

[redacted]



[redacted]

6.2. Scientific Rationale for Study Design

The study is a Phase 2, single-blind (subject and MRI analyst blind), 5-period, single-group oral daily dosing pilot study conducted at 2 sites. The 5 periods (in order) are screening, placebo, NYX-2925 20 mg, NYX-2925 200 mg, and follow-up. This is the first study of NYX-2925 in subjects with fibromyalgia. The key endpoints are derived from neuroimaging measurements. The study is single blind to assure that subjects in the study are not influenced by knowledge of the treatment they are receiving. Similarly, individuals involved in handling the neuroimaging data prior to the final statistical analyses will be blinded to the treatment period from which these data are collected. A full double blind was not considered necessary to protect against bias on the neuroimaging endpoints. [redacted]

group design. Each subject will receive 2 weeks of placebo, to measure the effects of placebo. Each subject will receive 2 weeks of treatment with NYX-2925 20 mg, followed by 2 weeks of treatment with NYX-2925 200 mg. This duration of treatment is well-supported by the 1 week duration of treatment in the NYX-2925-1001 multiple ascending dose study, which included [redacted]

6.3. Justification of Dose

The planned doses of NYX-2925 are 20 mg a day and 200 mg a day [redacted]

The 20 and 200 mg dose strengths of NYX-2925 planned for this study are expected to produce C_{max} plasma concentrations ranging from approximately 340 to 3400 ng/mL. T[redacted]

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject Inclusion Criteria

1. Female subjects 18 - 70 years of age.
2. Subject meets the 2010 American College of Rheumatology (ACR) criteria for fibromyalgia.
3. Self-reported clinical pain ≥ 4 and on the NPRS at screening at screening and baseline and consistent pain score collection during screening.
4. Subject receives and agrees to remain on their stable fibromyalgia treatment plan [redacted]
5. Subject agrees to use only non-steroidal anti-inflammatory (NSAID) or acetaminophen treatment as needed for breakthrough pain, and/or protocol specified medications for sleep (if needed).
6. Right handed.
7. Creatinine clearance ≥ 60 mL/minute calculated by the Cockcroft-Gault equation.
8. Female subjects of child bearing potential with a negative serum pregnancy test prior to entry into the study and who are practicing an adequate method of birth control ([redacted]
[redacted]
9. Ability to understand the requirements of the study, provide written informed consent, abide by the study restrictions, and agree to return for the required assessments.

7.2. Subject Exclusion Criteria

1. Current or expected use of opioid or narcotic analgesics [redacted]
2. Unstable doses of allowed gabapentinoids, topiramate, tramadol, antidepressants, or muscle relaxants. Use of NSAIDs or acetaminophen 24 hours prior to imaging procedures is prohibited.
3. Pain due to concurrent autoimmune or inflammatory disease [redacted]
4. Untreated endocrine disorder that may confound fibromyalgia assessments.

5. Psychiatric or cognitive disorder [redacted]
6. Clinically significant alcohol or other substance abuse within the last 2 years, in the opinion of the investigator.
7. Positive screen for medically inappropriate or illegal use of drugs of abuse including [redacted]
8. Current treatment with NMDAR ligands including ketamine, amantadine, dextromethorphan, memantine, methadone, dextropropoxyphene, or ketobemidone.
9. History of allergy, sensitivity, or intolerance to NMDAR ligands including ketamine, amantadine, dextromethorphan, memantine, methadone, dextropropoxyphene, or ketobemidone.
10. Women, who are pregnant, breast feeding, or planning to become pregnant or donate ova during the course of the study and for 28 days after the final administration of investigational product.
11. Any impairment, activity or situation that in the judgment of the investigator would prevent satisfactory completion of the study protocol. This includes unreliable or inconsistent pain scores, or an inability to tolerate the MRI procedure during screening.
12. Huntington's, Parkinson's, Alzheimer's, Multiple Sclerosis, or a history of seizures, epilepsy, or strokes.
13. Contraindications to fMRI procedures. [redacted]
14. Current or habitual use (within the last 12 months) of artificial nails, nails enhancements, or nail extensions that cover any portion of either thumbnail. Exceptions include brief and/or occasional use, may be permissible at the discretion of the investigator.
15. Abnormal laboratory results, medical history, or concurrent conditions that, in the opinion of the investigator or sponsor designated medical monitor, would preclude safe study participation, or interfere with study procedures/assessments.
16. Impaired hepatic function such as a known diagnosis of chronic liver disease [redacted]
17. Subjects with history of severe renal impairment defined by renal dialysis or peritoneal dialysis, or who have undergone renal transplant.
18. Known history of significant cardiovascular condition [redacted]

19. Current evidence of dysplasia or history of malignancy [redacted]
20. Human immunodeficiency virus (HIV) infection, hepatitis, or other ongoing infectious disease that the investigator considers clinically significant.
21. History of severe renal or hepatic impairment, in the opinion of the investigator or the sponsor designated medical monitor.
22. History of photosensitive migraine or migraine with aura, which in the opinion of the investigator, would be contraindicated in MRI procedures.
23. History of lower limb vascular surgery or current lower limb vascular dysfunction that would interfere with MRI procedures, in the opinion of the investigator.
24. Received an investigational drug or device within 30 days (or 5 half-lives, whichever is longer) of dosing.
25. Previous treatment with NYX-2925.
26. Resting heart rate < 45 or ≥ 95 beats per minute.

7.3. Screen Failures

Subjects who sign and date the informed consent form (ICF) but who fail to meet the inclusion and exclusion criteria are considered screen failures. Reason(s) for screen failure must be documented by the investigator and provided to the sponsor in a timely fashion. Subjects the investigator considers appropriate for the study may be rescreened.

7.4. Subject Withdrawal Criteria

Subjects who withdraw from the NYX-2925 treatment period will be not be replaced. Any subject may withdraw consent at any point during the study. The investigator can discontinue a subject at any time if it is deemed medically appropriate, or for subject noncompliance with study requirements. Subjects will be withdrawn from the study if any of the following criteria are met:

[redacted]

[redacted]

7.5. Methods of Birth Control

Female subjects of non-childbearing potential include those who are post-menopausal (at least 1 year without any menses prior to screening) or surgically sterile.

Female subjects of childbearing potential who are sexually active with a male partner must practice effective birth control starting at screening and continuing throughout the study period and for 28 days after the final administration of investigational product (IP). Methods of effective birth control include:

- Oral or parenteral contraceptives
- Intrauterine device (either hormonal or non-hormonal type) that is considered safe for MRI procedures.
- Barrier
- Abstinence

All female subjects of child bearing potential must have a negative serum pregnancy test at Screening and Baseline (if greater than 14 days since Screening visit).

8. STUDY TREATMENT

8.1. Dosing and Administration

Subjects will be given 2 weeks of placebo; then 2 weeks of NYX-2925 20 mg PO QD; then 2 weeks of NYX-2925 PO QD 200 mg for daily administration.

8.2. Investigational Product, Appearance, Packaging, and Labeling

[redacted]

Matching placebo capsules will contain only inactive ingredients listed previously.

Each bottle of IP will include 30 capsules of 10 or 100 mg NYX-2925, or matching placebo. The labels will include a kit number, capsule count, storage conditions, retest date, sponsor name, and investigational use statement. The sponsor will provide the investigative site with sufficient amounts of IP to conduct the study.

8.3. Preparation and Handling

The investigator will delegate IP handling, and accountability to a pharmacist or designee who will dispense bottles of IP (appropriate to the study period) for subject administration. Refer to the Product Pharmacy Manual for additional instruction.

8.4. Storage

IP should be stored in a locked, limited access location according to the label. The capsules should be stored at 20°C – 25°C with excursions permitted between 15°C – 30°C. The investigative site should contact the sponsor for directions regarding non-permitted excursions. Additional information may be provided in a Product Pharmacy Manual.

8.5. Accountability

The investigator will delegate IP accountability to the study pharmacist and/or designee. The investigative site personnel will receive, inspect, and acknowledge condition of IP; document the amount received, dispensed and returned, and will dispense, and maintain the IP accountability records. A sponsor representative will inspect IP and/or accountability records. Site personnel will conduct subject level accountability, account for and document used/unused IP, and maintain any unused IP (if applicable).

Prior to completion or termination of the study, all used and unused supplies will be returned or destroyed as specified in a Product Pharmacy Manual approved by a sponsor representative.

8.6. Treatment Compliance

Site personnel will record subject-reported administration and noncompliance with IP dosing; incorrect or partially administered doses will also be documented.

8.7. Randomization and Blinding

There is no randomization in this study. Matching placebo capsules will be administered during the placebo period so that subjects will be blinded. The investigator, pharmacy, and study clinicians will not be blinded; however, the site personnel involved with conducting imaging procedures and/or interpretations will not be informed regarding treatment period associated with corresponding imaging procedures. Sponsor personnel will not be blinded.

8.8. Concomitant and Excluded Medications

For the duration of the study, subjects must agree to remain on their stable fibromyalgia treatment plan established prior to study participation. Stable is defined as treatment with medication(s) and/or intervention(s) at the same prescribed dose established at least 14 days prior to study drug dosing.

[redacted]

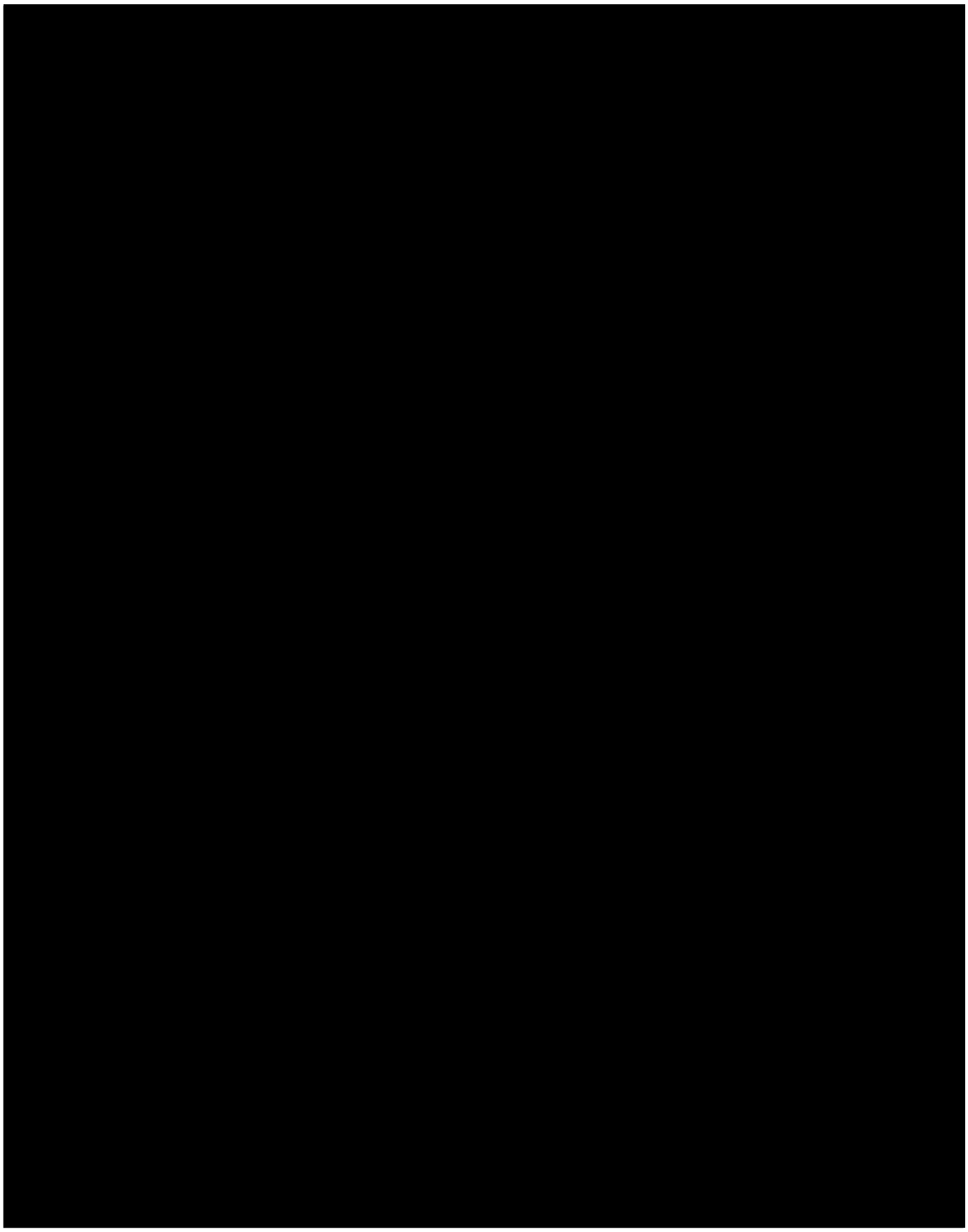
Breakthrough pain may be treated with NSAIDs or acetaminophen; however, use of NSAIDs or acetaminophen 24 hours prior to study visits that include imaging is prohibited.

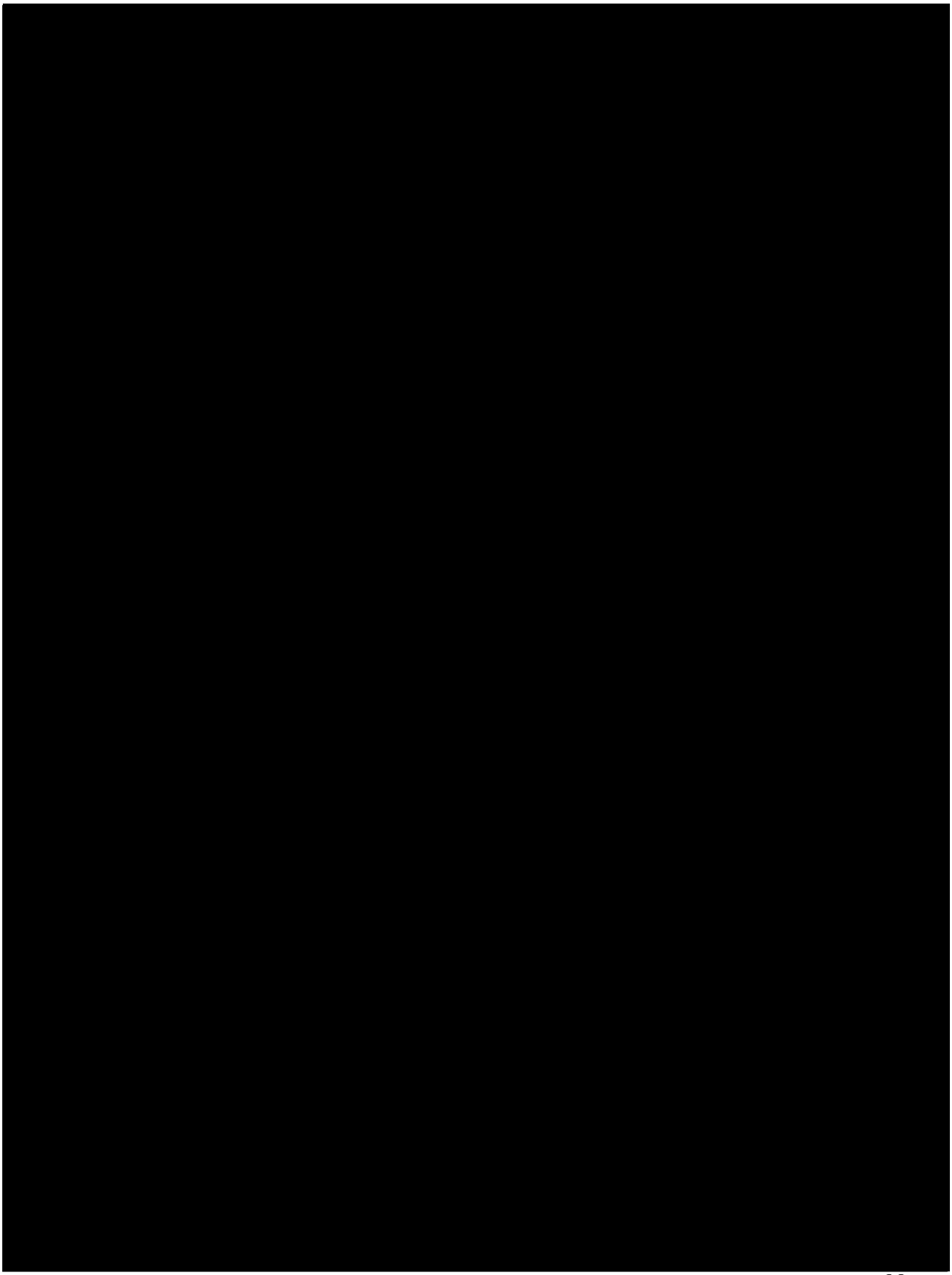
[redacted]

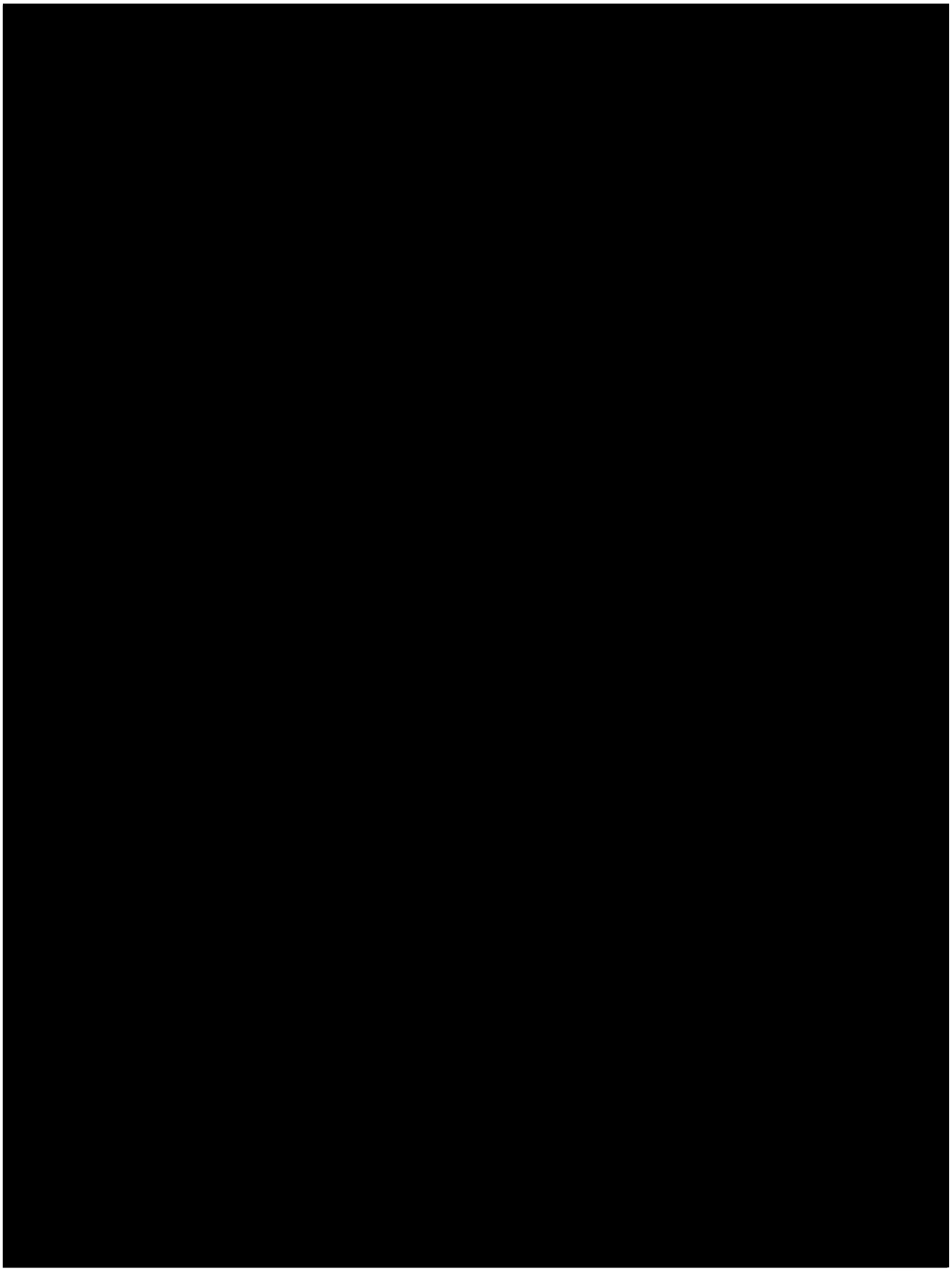
Concomitant medications used within 30 days prior to dosing and through the follow-up visit must be documented in the source documents and on the corresponding electronic case report form (eCRF).

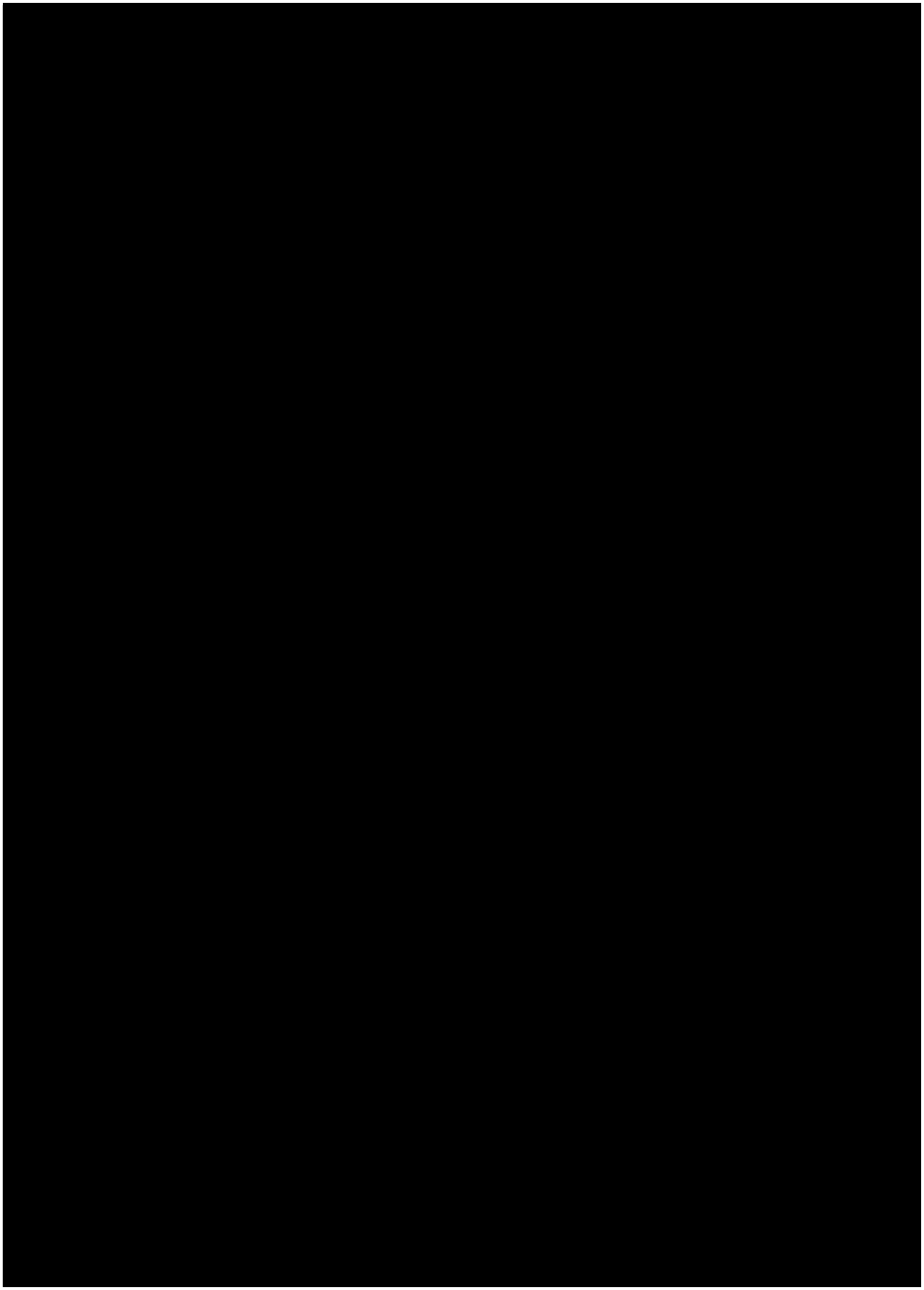
9. STUDY ASSESSMENTS AND PROCEDURES

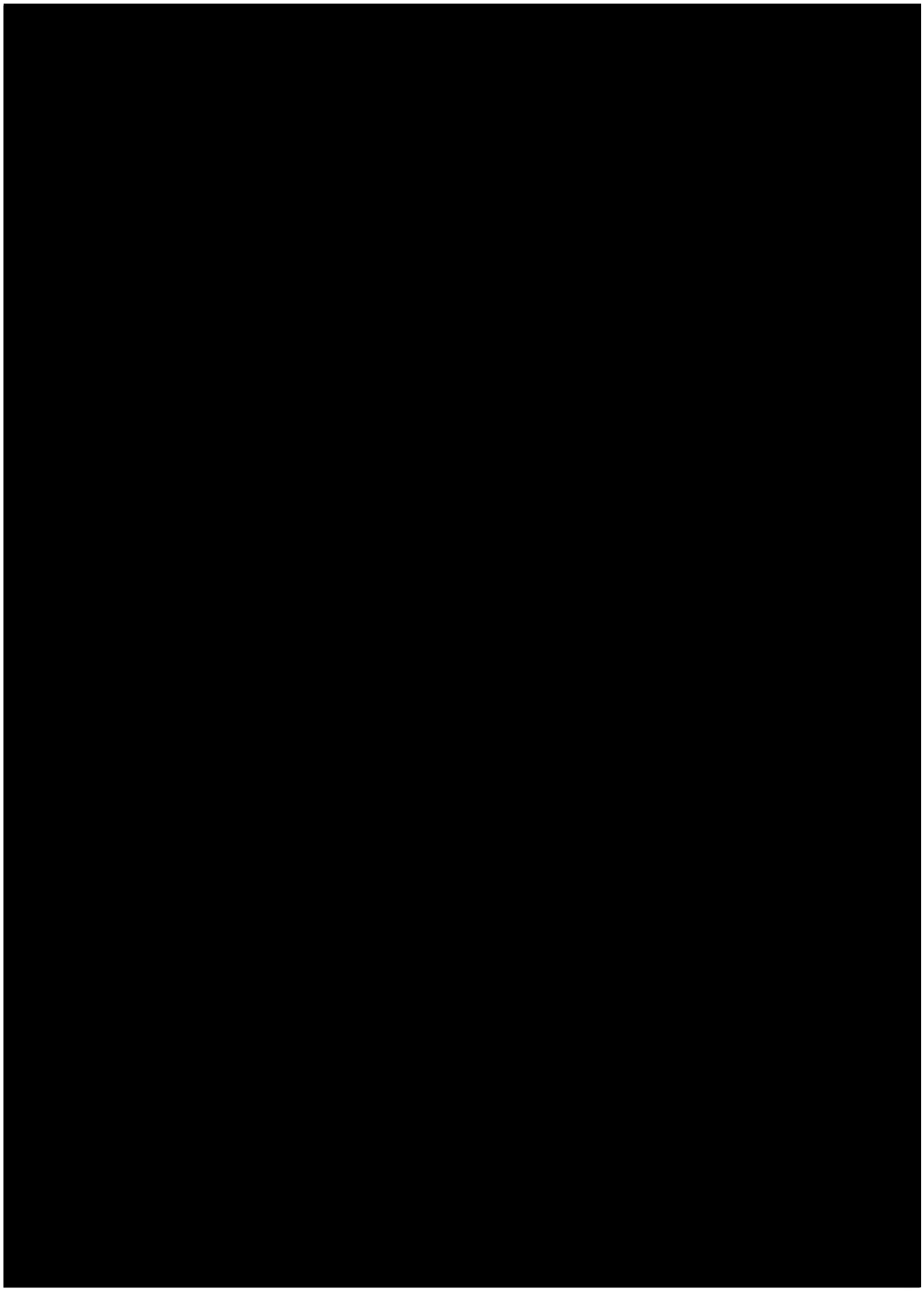
[redacted]











[redacted]

[redacted]

[redacted]

[redacted]

9.5. Safety and Pharmacovigilance

9.5.1. Adverse Events – Relationship to Study Drug

An AE 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 IP, regardless of causal relationship. 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 AE only if the frequency, intensity, or character of the pre-existing condition worsens during the course of the study.

Laboratory abnormalities are not considered AEs 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, coagulation, hematology, urinalysis) that is independent from the underlying medical condition and that requires medical or surgical intervention, or leads to IP interruption or discontinuation, must be considered an AE.

For each reported AE, an investigator must assess the relationship to study drug using the following scale:

Unrelated

- Does not follow a known response pattern to the suspect study drug (if response pattern is previously known).
- Can clearly be explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

Unlikely Related

- The temporal sequence from dosing of the study drug suggests that a relationship is unlikely.
- Follows a response pattern that is unlike that of the suspect study drug (if response pattern is previously known).
- Could be reasonably explained by the subject's clinical state or other modes of therapy administered to the subject.

Possibly Related

- Follows a reasonable temporal sequence from dosing of the study drug.
- May follow a known response pattern to the suspect study drug (if response pattern is previously known).

- Could also be reasonably explained by the subject's clinical state or other modes of therapy administered to the subject.

Probably Related

- Follows a reasonable temporal sequence from dosing of the study drug.
- Could not be reasonably explained by the known characteristics of the subject's clinical state or any other modes of therapy administered to the subject.
- Is confirmed by improvement on stopping or slowing dosing of the study drug, if applicable.

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

9.5.2. 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 AE only if the frequency, intensity, or character of the pre-existing condition worsens during the course of the study. Adverse events will be collected from the time the informed consent is signed to the end of the subject's participation in the study.

Subjects should be instructed to report all potential AEs to the investigator, and, queried in a non-leading 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 NMDA 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 AEs.

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

9.5.3. Reporting Adverse Events

All AEs must be documented, evaluated, and reported in the source documents and eCRF. Adverse event collection begins after the subject has completed the informed consent and continues until the subject's participation in the study ends. Ongoing adverse events should be followed to a satisfactory resolution in the investigator's opinion. Subjects should be instructed to report all AEs 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 AEs should be recorded on the eCRF. All clearly related signs, symptoms, and results of diagnostic procedures performed in relation to an AE should be grouped together and recorded as a single diagnosis.

9.5.4. Severity of Adverse Events

All AEs 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 AE 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).

9.5.5. Action Taken for Adverse Events

For each reported AE, an investigator must document the action taken according to the following criteria:

- No action taken
- Concomitant medication taken
- Hospitalization or prolongation of hospitalization
- Discontinued study
- Nondrug therapy
- Other (specify)

The investigator must also document the action taken in regards to IP (as a result of a given AE) according to the following criteria:

- Dose not changed
- IP interrupted
- IP withdrawn
- Not applicable
- Unknown

9.5.6. Outcome for AEs

AEs should be followed until resolution. For each reported AE, 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

9.5.7. Serious Adverse Event (SAE) Reporting

SAEs are reported to the sponsor-designated medical monitor using the Aptinyx provided form by email or fax at:

[redacted]

An SAE is any AE occurring at any dose that results in any of the following outcomes:

- Death: "Death" is an outcome and is NOT the AE. In the event of death, the cause of death should be recorded as the AE. The only exception is "sudden death" when the cause is unknown.
- Is a life-threatening experience: Life-threatening AEs include any adverse drug experience, which, 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 an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously. Example: allergic bronchospasm requiring intensive treatment in an emergency room or at home.

All SAEs 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 SAE report must be received within 1 business day.

All other SAEs or other events reportable to the United States Food and Drug Administration (FDA) and/or institutional review board (IRB) will be forwarded to the sponsor designated medical monitor within 1 business day.

The SAE report should provide as much of the required information as is available at the time. The following minimum information is required for reporting an SAE: 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 an SAE, the information will be treated as an SAE for the purposes of this protocol. Serious AE reporting will begin at the time of consent and will end 30 days after the last dose.

All relevant documentation pertaining to an SAE (additional laboratory tests, consultation reports, discharge summaries, postmortem reports, etc.) will be provided to the sponsor-designated medical monitor in a timely manner. Serious AEs will be followed until resolution or return to Baseline (when worsening of a pre-existing condition is reported). If an SAE does not return to Baseline but reaches a stable situation that is not expected to change, this may be documented on the SAE form.

9.6 Other Reportable Events

Reports of overdose (with or without an AE), abuse, dependency, inadvertent or accidental exposure, pregnancy, and unexpected therapeutic benefit should be forwarded in the same time frame as an SAE. Overdose occurs when a subject is dosed or has taken a dose greater than the intended or scheduled dose specified by the protocol. 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.

10. SCHEDULE OF PROCEDURES

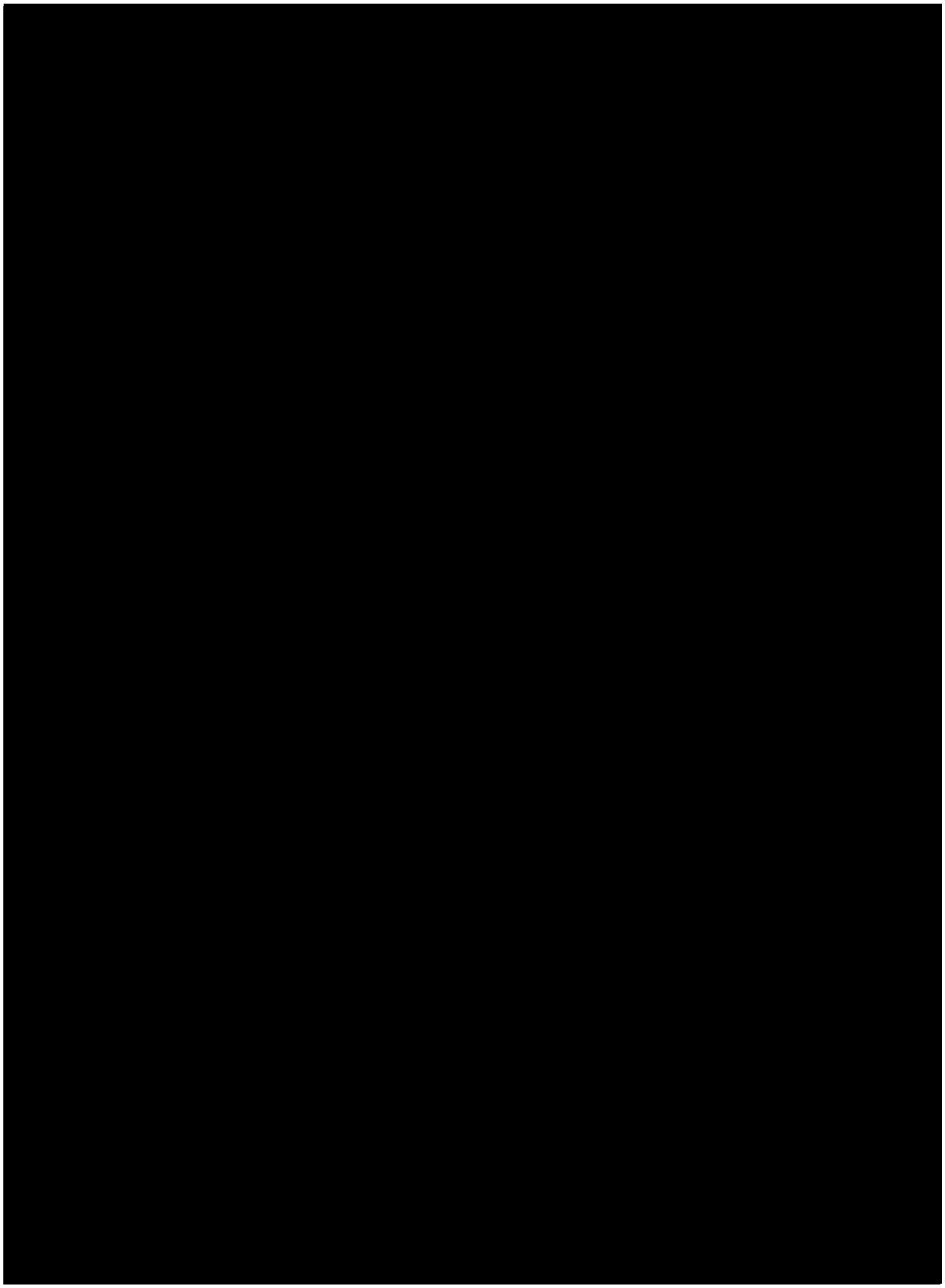
10.1. Screening Period (Days - 30 to -1)

Subjects will complete the following procedures after fasting for at least 10 hours prior to clinical laboratory assessments.

The magnetic resonance imaging procedures may be completed at any time during the screening period. If a subject is washing out of prohibited medication, the imaging must be performed after the washout has been completed. Use of NSAIDs or acetaminophen within 24 hours of imaging visit is prohibited.

- ICF
- Eligibility: inclusion/exclusion

[redacted]



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[redacted]

[redacted]

[redacted]

[redacted]

11. INDIVIDUAL STOPPING CRITERIA

Subjects will be withdrawn from the treatment period of the study if the following laboratory results are confirmed by repeat testing. Repeat testing must be completed within 48-72 hours:

12. STATISTICS

12.1. Sample Size Determination

The sample size was based on clinical considerations rather than statistical power.

12.2. Statistical Analysis Plan

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be finalized before the study has completed. Additional statistical analyses other than those described in this section may be performed if deemed appropriate and will be described in the SAP.

Descriptive statistics for categorical endpoints will include the number and percent of subjects in each category. Quantitative endpoints will be summarized with the mean, median, standard deviation, minimum value, and maximum value.

All data will be displayed in individual subject listings.

12.3. Analysis Populations

The safety population will consist of all subjects who receive at least 1 dose of study drug, whether NYX-2925 or placebo.

The efficacy population will consist of all subjects in the safety population with MRI measurements at baseline and following treatment with placebo and NYX-2925 20 mg.

12.4. Accountability and Baseline Characteristics

The number and percent of subjects who are treated with study drug, prematurely discontinue, and complete the study will be summarized. The number and percent of subjects will be summarized for each reason for premature discontinuation, overall and by study period.

Demographic data will be summarized descriptively for each analysis population.

12.5. Analyses of Efficacy

The following changes in efficacy endpoints will be summarized descriptively:

- Change from baseline to each scheduled evaluation after baseline, with baseline defined as the last evaluation prior to dosing with study drug on Day 1.
- Change from end of the placebo period to scheduled evaluations during each NYX-2925 period.
- Change from end of each NYX-2925 period to scheduled evaluations during the placebo follow-up period

Change to scheduled evaluations will be assessed with the paired t-test and signed rank test.

12.6. Analyses of Safety

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

12.6.1. Adverse Events

A treatment-emergent AE (TEAE) is defined as an AE with an onset that occurs after receiving study drug, or a continuing AE diagnosed prior to the date of first dose of study drug, which 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.

Summary tables for TEAEs will include numbers and percentages 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 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 for each study period (placebo, NYX 2925 20 mg, NYX-2925 200 mg, and follow-up:

- 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, and TEAEs leading to study drug discontinuation will be identified.

12.6.2. Clinical Laboratory Tests

Clinical laboratory results considered clinically important by the investigator will be identified.

Individual results of clinical laboratory tests from hematology, serum chemistry, and urinalysis outside of the normal range will be flagged in the data listings.

12.6.3. ECG

ECG results considered clinically important by the investigator will be identified.

12.6.4. Vital Sign Measurements

Change from baseline to each scheduled measurement will be summarized descriptively. Baseline will be defined as the last evaluation prior to dosing with study drug on Day 1.

12.6.5. Other Safety Data

Clinically significant deteriorations in physical examination will be recorded as adverse events.

12.6.6. C-SSRS

Subjects with suicidal ideation will be identified. Suicidal ideation will be defined as a "yes" answer at any time after the first dose of study drug to any of the 5 suicidal ideation questions on

the C-SSRS. Data collected for C-SSRS will be summarized by treatment and visit/time point. Change from Baseline, if applicable, will also be calculated and summarized in the same manner.

12.6.7. Interim Analysis

Interim analyses may be completed for this study. Given that the study is single-blind and Phase 2, there will be no adjustments to Type I error.

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, ICFs, clinical laboratory reports, imaging results, medical histories, hospital records, and drug accountability records. All source documents will be maintained by the investigator(s) and made available for inspection by sponsor representatives, the FDA, and other applicable regulatory authorities.

13.2. Study Monitoring

Site visits will be conducted by an authorized sponsor representative (site monitor) to inspect study data, source documents, and eCRFs in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, good clinical practices (GCPs), 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.

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

13.3. Case Report Forms

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

13.4. Protocol Amendment(s)

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

13.5. Audits and Inspections

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

13.6. Institutional Review Board/Independent Ethics Committee (IRB/IEC)

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

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

The investigator agrees that he or 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 protocol 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 participants prior to the initiation of non-routine study-related tests. The original signed ICF for each participating subject shall be filed with records kept by the investigators(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 ICF is revised, subjects must be re-consented 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, IP accountability records, 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, IP reconciliation activities are completed, study procedures and assessments are completed and source verified.

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 (PHI), and in accordance with applicable national and/or local laws and regulations on PHI 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 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 1 year after study completion.

13.14. Records Retention

According to US Investigational New Drug regulations (21 CFR 312.62), records and documents pertaining to the conduct of this study and the distribution of IPs including but not limited to source documents, eCRFs, ICFs, 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 at least 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 at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. Aptinyx will notify the investigator when records and documents no longer need to be retained. No study records should be destroyed without prior authorization from Aptinyx.

13.15. Publication Policy

The publication policy is outlined in the Clinical Trial Agreement.

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