TNX-102 SL (CYCLOBENZAPRINE HCL SUBLINGUAL TABLETS)

TNX-CY-PA201

A PHASE 2, 14-WEEK DOUBLE-BLIND, RANDOMIZED, MULTICENTER, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF TNX-102 SL TAKEN DAILY AT BEDTIME IN PATIENTS WITH MULTI-SITE PAIN ASSOCIATED WITH POST-ACUTE SEQUELAE OF SARS-COV-2 INFECTION (PASC)

"THE PREVAIL STUDY"

Protocol Amendment 2 Release Date: 13 Oct 2022

Replaces Protocol Amendment 1 Release Date: 29 Apr 2022

Original Protocol Release Date: 24 Nov 2021
US IND No. 156272

Sponsor:
Tonix Pharmaceuticals, Inc. (Tonix)
[redacted]

For Tonix:

[redacted]

TONIX PHARMACEUTICALS

TNX-102 SL (CYCLOBENZAPRINE HCL SUBLINGUAL TABLETS)

TNX-CY-PA201

A PHASE 2, 14-WEEK DOUBLE-BLIND, RANDOMIZED, MULTICENTER, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF TNX-102 SL TAKEN DAILY AT BEDTIME IN PATIENTS WITH MULTI-SITE PAIN ASSOCIATED WITH POST-ACUTE SEQUELAE OF SARS-COV-2 INFECTION (PASC)

"THE PREVAIL STUDY"

Protocol Amendment 2 Release Date: 13 Oct 2022

Replaces Protocol Amendment 1 Release Date: 29 Apr 2022

Original Protocol Release Date: 24 Nov 2021

US IND No. 156272

[redacted]

INVESTIGATOR'S AGREEMENT

I have read the TNX-CY-PA201 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		

2. SYNOPSIS

Name of Sponsor/Company:
Tonix Pharmaceuticals, Inc.

Name of Investigational Product:
TNX-102 SL (Cyclobenzaprine HCl Sublingual Tablets)

Name of Active Ingredient:
Cyclobenzaprine HCl

Title of Study:

A Phase 2, 14-week Double-Blind, Randomized, Multicenter, Placebo-Controlled Study to Evaluate the Efficacy and Safety of TNX-102 SL Taken Daily at Bedtime in Patients with Multi-site Pain Associated with Post-Acute Sequelae of SARS-CoV-2 Infection (PASC) (Protocol No. TNX-CY-PA201)

Study center(s): Approximately 30 centers in the United States

Estimated Studied period: 16 months Estimated date first patient enrolled: August 2022 Estimated date last patient completed: November 2023	**Phase of development:** 2

Objectives:

Primary

To evaluate the efficacy of TNX-102 SL 5.6 mg daily at bedtime in the treatment of patients with multi-site pain associated with Long COVID.

Secondary

To evaluate the safety and tolerability of TNX-102 SL 5.6 mg daily at bedtime in the treatment of multi-site pain associated with Long COVID.

Methodology:

This is a Phase 2, randomized, parallel-group, double-blind, placebo-controlled, 14-week study designed to evaluate the efficacy and safety of TNX-102 SL 5.6 mg (2 x 2.8 mg tablets) taken once daily at bedtime for the management of multi-site pain associated with Long COVID. The study is to be conducted at approximately 30 investigational sites in the United States.

The study will consist of a Screening Visit (Visit 1, Days -35 to -7), a Washout and Screening period of at least 7 days (for those patients not requiring washout) and no more than 35 days, inclusive of a 7-day baseline data collection phase immediately preceding the Baseline Visit. Eligible patients who provide written informed consent will have study assessments performed at Screening. Due to limitations in the diary completion window, patients who are planning on

international travel during the study period should not be considered for the study. Patients whose employment involves overnight shifts also should not be considered for the study due to the restricted completion window and the requirement for consistent bedtime dosing.

At Screening Visit 1 and after signing the written informed consent, any required washout should be discussed with the patient and plans made for an appropriate schedule for reducing/stopping any excluded medications. This down-titration and discontinuation of excluded medications must be accomplished so that the patient is free of excluded medications at least 14 days prior to beginning of the collection of Baseline diary data that takes place during the 7 days leading up to the Baseline/Randomization Visit. Any additional time required for down-titration would be in addition to this washout requirement. For extenuating circumstances, the total duration of the Screening period may be increased to up to a maximum of 49 days with Medical Monitor approval. All excluded medications will be stopped during the Washout period through Week 14/Early Termination Visit (ET) (Visit 6).

Pre-randomization Approval by Tonix Pharmaceuticals will be required prior to the Baseline/Randomization Visit (Visit 2) in addition to satisfying all other eligibility and randomization criteria.

The Screening period will be followed by the Baseline/Randomization Visit (Visit 2, Day 1), and 4 in-clinic visits at Weeks 2, 6, 10, and 14/ET. Due to the exceptional circumstances caused by the COVID-19 pandemic, an option for a telephone visit will be available for Weeks 2, 6, 10 (Visits 3, 4, 5), and, only with Medical Monitor approval, Week 14/Visit 6 (or ET) for those unable to attend an in-clinic visit due to the COVID-19 pandemic. Approximately 2 weeks after Week 14 (Visit 6), there will be an initial Post-study Safety Follow-up telephone call (Visit 7), and approximately 4 weeks after Week 14, there will be a 1-Month Safety Follow-up telephone call (Visit 8). The total duration for each individual participant in the study, including Screening, may be as long as 25 weeks. The maximum treatment duration will be 14 weeks.

Patients will be trained on use of the electronic diary (eDiary) system at Visit 1. During the 7-day run-in Phase (7 days immediately preceding Visit 2 [Baseline/Randomization Visit; Day 1]) patients will be asked to record their worst daily Long COVID pain intensity on the 11-point (0−10) numeric rating scale (NRS) scale using 24-hour recall and assess sleep quality from the previous evening, also using an 11-point NRS scale. The average of the 7 days immediately preceding Visit 2 (Baseline Randomization Visit; Day 1) will serve as the Baseline pre-treatment scores.

After completing any required washout of excluded therapies and recording Baseline Diary scores for at least 7 days, patients will return to the investigative site for Baseline assessments and randomization (Day 1, Visit 2), when they will be randomly assigned to receive TNX-102 SL or matching placebo sublingual tablet in a 1:1 ratio.

Patients will take the study drug sublingually (SL) once daily at bedtime, starting on the day of randomization (Day 1), for 14 weeks. For the first 2 weeks of treatment, patients will start on TNX-102 SL 2.8 mg/day (1 tablet) or placebo.

All patients will then return to the clinic at Week 2 (Visit 3) for efficacy and safety assessments and assessment of study drug compliance. The study drug dose will be increased to 2 tablets (5.6 mg; 2 x 2.8 mg of TNX-102 SL or placebo) taken sublingually and simultaneously daily at

bedtime. Patients will next return to the clinic at Week 6 (Visit 4) for assessment of safety, efficacy, study drug compliance, and dose tolerability at the 5.6-mg daily dose. In scenarios in which TNX-102 SL 5.6 mg (or 2 placebo tablets) is considered intolerable due to adverse event(s) (AEs) and would otherwise lead to study discontinuation, with Medical Monitor approval, the Investigator may lower the dose back to 1 tablet every night (TNX-102 SL 2.8 mg or 1 placebo tablet). If/when it is deemed clinically warranted by the Investigator, re-challenge with 2 tablets TNX-102 SL 2.8 mg (5.6 mg dose)/placebo may be attempted, or the patient may remain on the lower dose for the remainder of the study. Patients will return to the clinic for safety, tolerability, and efficacy assessments, and assessments of study drug compliance at Weeks 10 (Visit 5) and 14 (Visit 6) or ET and will receive two safety follow-up calls approximately 2 weeks (Visit 7) and 4 weeks (Visit 8) later.

During the treatment phase, each evening, the eDiary will prompt the patient to reflect on the past 24 hours and record their worst pain intensity, assess their sleep quality from the previous evening, and log study drug dosing from the previous night (post-randomization).

Patients who wish to withdraw from the study may do so at any time.

Number of Patients (planned):

Approximately 470 patients (235 per arm) will be randomized in a 1:1 ratio to treatment with TNX-102 SL or placebo tablets. Randomized patients who withdraw will not be replaced.

Diagnosis and main criteria for inclusion:

Inclusion criteria (assessed at screening [Visit 1]):

1. The patient is male or female, 18 to 65 years of age, inclusive.
2. The patient has a confirmed history of SARS-CoV-2 infection at least 3 months prior to enrollment, based on a documented written positive viral test at the time of active infection through either a polymerase chain reaction (PCR) or nucleic acid tests or a rapid antigen test. Acceptable documentation of SARS-CoV-2 infection may be through either a laboratory report or formal documentation either generated at the point-of-care or by a virtual at-home test proctor/telehealth service.
3. The patient has a history of COVID-19 infection with a grading of 1 to 6 on the World Health Organization (WHO) COVID-19 8-Category Ordinal Scale of Disease Severity (Appendix 1).
4. The patient has new onset or significant worsening of pain that coincides with a prior COVID-19 infection. The new or worsening pain following COVID-19 infection has been generally present for at least 3 months post initial COVID-19 diagnosis, but no longer than 18 months post initial COVID-19 diagnosis.
5. The patient meets criteria for multi-site pain as defined by the modified Michigan Body Map (mMBM) closely following the SARS-CoV-2 infection, which includes:
    - Multi-site pain, characterized as pain in at least 4 out of 7 body regions (mMBM Part 2, Appendix 2)

6. The patient's in-clinic 7-day recall NRS average daily Long COVID pain intensity score at Screening Visit must be ≥ 4 and ≤ 9 (Appendix 3). Exceptions are only possible with Medical Monitor's approval.
7. The patient has a Post-COVID-19 Functional Status Scale (PCFS) score of ≥ 2 (Appendix 4) at Screening and Baseline.
8. The patient does not have another disorder that would otherwise explain his/her pain.
9. If female, is either not of childbearing potential (defined as postmenopausal for at least 1 year or surgically sterile [eg, bilateral oophorectomy or hysterectomy]) or will be practicing one of the following methods of birth control throughout the study and for 28 days after study drug discontinuation:
   a. Hormonal methods such as oral, implantable, injectable, or transdermal contraceptives for a minimum of one full cycle (based on the patient's usual menstrual cycle period) before study drug administration;
   b. Intrauterine device;
   c. Bilateral tubal ligation
   d. Double-barrier method (condoms, sponge, diaphragm, or vaginal ring with spermicidal jelly or cream);
   e. Partners of vasectomized males in stable relationships;
   f. Females involved in same-sex relationships;
   g. Female patients practicing abstinence may have the birth control requirement waived only with Medical Monitor approval.
10. If the patient is vaccinated against the SARS-CoV-2 virus, the patient is at least 2 weeks past a vaccine dose.
11. If the patient is currently receiving any non-exclusionary pharmacologic treatments, the patient should be on stable doses of their treatment regimen for at least 4 weeks (except for allowed antidepressants, which require 90 days at stable dose) prior to randomization and should not be expecting dosing change during the period of the trial.
12. The patient must be willing and able to withdraw from the following therapies for the duration of the study: duloxetine, milnacipran, pregabalin, gabapentin, tramadol, tapentadol, amitriptyline and other tricyclic antidepressants, trazodone, narcotics/opioids, naltrexone (including CONTRAVE®), all other forms of cyclobenzaprine (AMRIX®, or generic equivalents), orexin receptor antagonists, and benzodiazepines.
13. The patient is willing and able to comply with all protocol-specified requirements.
14. The patient is capable of reading and understanding English and has provided written informed consent to participate.

Exclusion criteria (Assessed at the screening [Visit 1]):

1. The patient has been diagnosed with infectious or inflammatory arthritis (eg, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis), systemic lupus erythematosus, gout, or meets criteria for another type of systemic autoimmune disease (eg, Sjogren's disease).
2. The patient has been diagnosed with a complex regional pain syndrome, fibromyalgia, failed back surgery syndrome, persistent or prevalent pain symptoms related to systemic disease (eg, diabetic peripheral neuropathy, post-herpetic neuropathy), untreated hyperparathyroidism, or a history of prior surgery, trauma, organ or tissue damage, or other source of pain that, in the Investigator's opinion, would confound or interfere with

the assessment of the patient's symptoms or require excluded therapies during the patient's study participation.

3. The patient has any lifetime history of bipolar disorder, schizophrenia, schizoaffective disorder, or other psychotic disorder as determined at Screening either by history or by the Mini International Neuropsychiatric Interview, Version 7.0.2 (MINI 7.0.2) Module A (Major Depressive Episode), Module C (Manic and Hypomanic Episodes), Module K (Psychotic Disorders), and Module O (Rule Out Medical, Organic, or Drug Causes for All Disorders).
4. History of or evidence for a diagnosis of borderline personality disorder (BPD) based on a score of ≥ 7 on the McLean Screening Instrument for BPD (MSI-BPD) at Visit 1 (Screening).
5. The patient is at increased risk of suicide on the basis of the Investigator's judgment, or the results of the Columbia Suicide Severity Rating Scale (C-SSRS) conducted at Screening and Baseline (eg, any C-SSRS suicidal behavior or C-SSRS Type 3, 4, or 5 ideation during the preceding 6 months and any suicidal behavior within the past 12 months).
6. The patient has participated in any other study with TNX-102 SL.
7. The patient has a history of COVID-19 infection with a grading of ≥ 7 on the WHO COVID-19 8-Category Ordinal Scale of Disease Severity (Appendix 1).
8. Based on screening laboratory results, thyroid-stimulating hormone (TSH) > 1.5 times the upper limit of normal, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 times the upper limit of normal, or glycated hemoglobin (HbA1c) > 7.5%; or, in the Investigator's opinion, evidence of a clinically significant laboratory abnormality based on Screening laboratory tests or medical history.
9. Diagnosed with clinically significant and currently relevant cardiac disease (eg, significant arrhythmia; heart block; heart failure; symptomatic coronary artery disease or orthostatic hypotension), recent myocardial infarction [within the past 2 years]) or QTcF > 450 msec (male) or > 470 msec (female) on the screening electrocardiogram (ECG).
10. The patient currently has or has a history of a clinically significant systemic viral infection (eg, human immunodeficiency virus [HIV], hepatitis B or C).
11. The patient is currently receiving or is expected to need systemic corticosteroids (> 5 mg prednisone or equivalent per day) or has received acute treatment with systemic corticosteroids within 28 days of the Baseline Visit, or is likely to require such treatment during the study.
12. The patient has received tender point, trigger point, or other local injections with anesthetic agents (or corticosteroids, as per Exclusion Criterion #11) within 28 days of the Baseline Visit, or is unable to refrain from such injections during the study.
13. The patient is unable to successfully washout of the following medications during Screening, or washout is inadvisable: monoamine oxidase inhibitors (30-day washout required), levomilnacipran, anticonvulsants (aside from those used as migraine prophylaxis), amphetamine mixed salts, weight loss agents such as phentermine and diethylpropion, muscle relaxants (eg, methocarbamol, baclofen, carisoprodol, cyclobenzaprine), stimulants (eg, methylphenidate, lisdexamfetamine, dextroamphetamine), mirtazapine, trazodone, nefazodone, St. John's wort, any medication known to be a strong CYP3A4 inhibitor (Appendix 5) or any of the medications listed in Inclusion Criterion #12.

14. Positive results for illegal or abused substances other than cannabis/THC at Screening or Baseline or history of substance use disorder during the preceding 1 year as defined by the screening MINI 7.0.2 Module J (Substance Use Disorder). Patients who utilize alcohol and/or cannabis/THC but do not meet criteria for greater than MILD Alcohol Use Disorder in Module I (Alcohol Use Disorder) and/or MILD Cannabis Use Disorder in Module J in the preceding 1 year are suitable for the study provided that, in the judgment of the Investigator, this usage will not interfere with the patient's ability to complete the study or provide reliable data.
15. Use of chewing or dipping tobacco or betel nut in the previous 6 months.
16. Planned use of teeth-whitening strips or prescription teeth-whitening products over the course of study participation.
17. Any existing oral, medical, or dental condition that could potentially interfere with the sublingual administration of study drug, the tolerability of study drug or with the evaluation of administration site reactions.
18. Any history of severe or unexplained oral or oropharyngeal swelling or edema.
19. The patient has any clinically significant, uncontrolled, or unstable medical or surgical condition that could affect his or her ability to participate in the study or potentially compromise his or her well-being during the study. Patients with history of malignancy within 5 years of screening (other than treated carcinoma *in situ* of the cervix, basal cell carcinoma, or Type 1 squamous cell carcinoma of the skin) must receive Medical Monitor approval prior to randomization.
20. The patient has an anticipated need for surgery that might confound results or interfere with his or her ability to comply with the protocol.
21. The patient is pregnant or nursing.
22. The patient has a hypersensitivity to cyclobenzaprine or the excipients in TNX-102 SL or placebo formulations or any contraindications to the use of cyclobenzaprine (such as history of urinary retention or increased intraocular pressure).
23. The patient has a seizure disorder or neuropathic pain that requires anticonvulsant therapy.
24. The patient has a history of sleep apnea that is severe, uncontrolled, or untreated. Patients with mild obstructive sleep apnea (eg, apnea/hypopnea index 5–15), and/or patients whose mild to moderate sleep apnea is well-controlled with continuous positive airway pressure or oral device, are allowed at the discretion of the Investigator.
25. The patient has a BMI > 38.0 kg/m^2 (due to the increased risk of sleep apnea).
26. The patient has a history of narcolepsy, cataplexy, restless leg syndrome, periodic involuntary limb movement disorder or other documented, clinically significant sleep disorder.
27. The patient has plans for international travel, or has a work schedule (eg, requiring night shifts), that prevents them from being able to utilize the diary system during its available time window or to take study medication on a regular basis.
28. The patient is currently being treated with immunosuppressive medication, sodium oxybate, ketamine, esketamine, or calcitonin gene-related peptide (CGRP) receptor antagonists.
29. The patient has received an investigational CGRP receptor antagonist within 90 days of Screening, or any other investigational drug within 30 days of Screening.

30. The patient is currently receiving other therapies to treat acute COVID-19 symptoms or severity, such as convalescent plasma, remdesivir, or dexamethasone
31. The patient has another active systemic bacterial or fungal infection, or the patient is taking medications to treat another type of active infection

Randomization criteria (assessed at Visit 2, Baseline):

Only those patients meeting all of the following randomization criteria are eligible for randomization:

1. Continues to meet all inclusion and exclusion criteria, including urine and blood test results, and is successfully and consistently utilizing the diary system.
2. Patient's pain satisfies the following criteria, as assessed by diary pain scores (24-hour recall):
   a. A mean worst daily Long COVID pain intensity score ≥ 4 and ≤ 9 on the 11-point (0−10) NRS for the 7 days immediately preceding Visit 2, and
   b. No more than 2 individual days with a Long COVID pain score < 4 on the 7 days immediately preceding Visit 2, and
   c. No score of 10 on any of the 7 days immediately preceding Visit 2, and
   d. Long COVID pain scores recorded on at least 5 out of the 7 days immediately preceding Visit 2.

Investigational product, dosage and mode of administration:

Name: TNX-102 SL (cyclobenzaprine HCl sublingual tablets)

Dose, route, frequency: For Days 1−14, 1 tablet of TNX-102 SL 2.8 mg taken sublingually (under the tongue) each day at bedtime. For Days 15−98, 2 tablets of TNX-102 SL 2.8 mg (5.6 mg) taken simultaneously and sublingually (under the tongue) each day at bedtime.

Duration of treatment:

14 weeks

Reference therapy, dosage and mode of administration:

Name: Placebo

Dose, route, frequency: For Days 1−14, 1 tablet of placebo taken sublingually (under the tongue) each day at bedtime. For Days 15−98, 2 tablets of placebo taken simultaneously and sublingually each day at bedtime.

Treatment Regimens:

Patients will take 1 tablet of randomly assigned study drug sublingually at bedtime once daily starting on Day 1 for 2 weeks; then patients will take 2 tablets of assigned study drug simultaneously and sublingually once daily starting on Day 15 for 12 weeks. A drink of water is recommended prior to dosing for patients with a dry mouth. Patients will be asked to keep the

tablet(s) under the tongue until dissolved (approximately 90 seconds) and not to crush or chew the tablets. Patients should not eat, drink, or chew gum for at least 15 minutes after dosing, and preferably not to drink any hot, cold, or acidic beverage until morning. Patients should also refrain from talking for at least 5 minutes after dosing.

In scenarios in which the daily dose of 2 tablets (5.6 mg) is considered intolerable and would otherwise lead to study discontinuation, with Medical Monitor approval, the Investigator may lower the dose to 1 tablet (2.8 mg) per day. If/when it is deemed clinically warranted by the Investigator, re-challenge with 2 tablets TNX-102 SL 2.8 mg (5.6 mg dose)/placebo may be attempted.

Criteria for Evaluation:

Efficacy:

Primary efficacy endpoint:

- Change from Baseline in the diary NRS weekly average of daily self-reported worst Long COVID pain intensity scores at the Week 14 endpoint.

Key secondary efficacy endpoints:

- Change from Baseline in the weekly average of the daily diary NRS assessment of sleep quality at the Week 14 endpoint
- Change from Baseline in the PROMIS score for fatigue at the Week 14 endpoint
- Change from Baseline in the PROMIS score for cognitive function at the Week 14 endpoint

Secondary efficacy endpoints:

- Change from Baseline in the Patient Reported Outcomes Measurement Information System (PROMIS) score for sleep disturbance at the Week 14 endpoint
- Proportion of patients with a Patient Global Impression of Change (PGI-C) rating of "very much improved" or "much improved" at the Week 14 endpoint
- Change from Baseline to Week 14 in the Sheehan Disability Scale (SDS)
- Change from Baseline to Week 14 in the Insomnia Severity Index (ISI)
- Change from Baseline to Week 14 in the Epworth Sleepiness Scale (ESS)

Exploratory efficacy endpoints:

- Proportion of patients with a ≥ 30% improvement from Baseline to Weeks 1−14 in the daily self-reported worst Long COVID pain intensity score
- Proportion of patients with a ≥ 50% improvement from Baseline to Weeks 1−14 in the daily self-reported worst Long COVID pain intensity scores
- Proportion of Patients with a PGI-C rating of "very much improved" or "much improved" at each post-randomization clinic visit
- PGI-C (1-7) rating at each post-randomization clinic visit

- Change from Baseline in the PROMIS score for sleep disturbance at each post-randomization clinic visits
- Change from Baseline in the PROMIS score for fatigue at each post-randomization clinic visits
- Change from Baseline in the PROMIS fatigue symptom questions 1,3,4 (individually and summed) at each post-randomization clinic visit
- Change from Baseline in the PROMIS fatigue impact questions 6,7,8 (individually and summed) at each post-randomization clinic visit
- Change from Baseline in the PROMIS score for cognitive function at each post-randomization clinic visits
- Change from Baseline in the weekly average of the daily diary assessment of sleep quality at Weeks 1−14
- Change from Baseline in the weekly average of the daily diary assessment of worst pain intensity scores at Weeks 1−14
- Change from Baseline in laboratory markers of inflammation
- Change from Baseline to Week 14 in the PCFS
- Change from Baseline in the total number of modified Michigan Body Map pain regions identified as having pain at each post-randomization clinic visit
- Change from Baseline in average NRS Long COVID pain intensity across the 7 pain regions in the modified Michigan Body Map at each post-randomization visit; regions without pain identified will be assigned a value of 0
- Change from Baseline in average NRS Long COVID pain intensity within the index site region on the modified Michigan Body Map at each post-randomization visit
- Change from Baseline in average NRS Long COVID pain intensity within the worst region for a given visit on the modified Michigan Body Map at each post-randomization visit; this will compare the value for the worst region at a visit and the worst region at baseline
- Subgroup analyses of the above endpoints by severity of their SARS-CoV-2 infection using groupings of the WHO ordinal scale of COVID severity as data allow
- Subgroup analyses of the above endpoints by COVID vaccine status

Safety:

- Incidence of AEs
- Changes from Baseline in clinical laboratory tests
- Changes from Baseline in vital signs
- Assessment of physical examination findings, including examination of the oral cavity
- Monitoring suicidality using Columbia Suicide Severity Rating Scale (C-SSRS)

Prior and Concomitant Medications:

Patients who are taking certain medications are eligible for the study if they are willing and able, and it is medically reasonable, for them to be withdrawn from these medications prior to

randomization and then refrain from usage during this study. The specific medications that must be withdrawn include duloxetine, milnacipran, pregabalin, gabapentin and other forms of anticonvulsants, tramadol, tapentadol, amitriptyline and other tricyclic antidepressants, trazodone, narcotics/opioids, naltrexone (including CONTRAVE®), all other forms of cyclobenzaprine (AMRIX®, or generic equivalents), orexin receptor antagonists, and benzodiazepines.

Therapies used to treat acute COVID-19 symptoms or severity, such as convalescent plasma, remdesivir, or dexamethasone will be prohibited. Due to the exclusion of all opioids (including tramadol and tapentadol) during the treatment phase of the study, patients requiring opioids on a regular or frequent basis for any indication should not be considered.

In addition, patients who are taking gabapentin, pregabalin, or any other anticonvulsant due to neuropathic pain should not be considered.

Other prescription or over-the-counter medication not specifically excluded by entry criteria may be continued during the study, provided that the patient has been on this medication a stable dose for at least 4 weeks (except for allowed antidepressants, which require 90 days at stable dose) prior to randomization and is not expecting to change dosages during the period of the study

In addition, certain other medications will also be prohibited and may require washout or exclusion of the patient if washout is not appropriate (eg, trazodone, mirtazapine, levomilnacipran, nefazodone, benzodiazepines, non-benzodiazepine sleep aids, stimulants, sodium oxybate, ketamine, esketamine, etc.).

Patients using teeth-whitening products such as whitening strips or prescription whitening products must agree to discontinue their use from the day of randomization until the end of their study participation.

After randomization, sedating antihistamines (eg, diphenhydramine, hydroxyzine) can be used as needed for insomnia; however, patients must be able to discontinue them during the Screening phase and must refrain from their use during the week of baseline data collection preceding Visit 2. The use of sedating anti-histamines after randomization should be under the direction of the Investigator, and such use should be minimized to no more than a few nights in a row, followed by attempts to refrain from use.

The use of non-prescription nutraceuticals such as melatonin, ramelteon, and valerian root is not restricted.

New medications that are deemed required, in the opinion of the Principal Investigator or another physician, will be allowed, including medications needed to treat AEs. If there is a requirement for acute opioids, corticosteroids, or other treatments that could confound the evaluation of pain throughout the treatment period, the Investigator may consult with the Medical Monitor to potentially delay the study visit until the medication is no longer needed. At a minimum, no opioid/narcotic should have been utilized within 2 days of a study visit, and ideally there will have been no usage during the 7 days prior to any visit, since important efficacy data will be collected on the eDiary.

Rescue medications used by patients throughout the study will be identified and documented during study visits.

Statistical methods:

Populations for Analysis:

In the case that the study goes to full enrollment or has a sample size increase, the following analysis populations are planned for this study:

- All patients: Used for summaries of dispositions of patients; tabulations of dispositions may also use the populations below.
- Safety population: all patients who receive at least one dose of the investigational product. All safety analyses will be performed using this population, analyzed as treated.
- Intention-to-treat (ITT) population: all patients who are randomized. This is the primary population for efficacy analyses, and patients will be analyzed based on their randomized treatment.

In the case of an early stop for efficacy or futility from the interim analysis, the following populations will be utilized:

- All Patients: used for summaries of dispositions of patients; tabulations of dispositions may also use the populations below.
- Interim Safety population: all patients who receive at least one dose of the investigational product and included in the cohort of interim analysis patients. All safety analyses will be performed using this population, analyzed as treated.
- Interim ITT population: all patients who are randomized and included in the cohort of interim analysis patients. This is the primary population for efficacy analyses, and patients will be analyzed based on their randomized treatment.
- Full Safety population: all patients who receive at least one dose of the investigational product. This will be used for supportive safety analyses on all patients exposed in the study, analyzed as treated.

Efficacy Analyses:

The primary efficacy parameter will be the difference between TNX-102 SL and placebo in the weekly mean change in worst pain score from Baseline to the Week 14. The weekly pain score will be based on the weekly average of the daily diary patient self-reported 24-hour recall worst Long COVID pain intensity scores using an 11-point (0−10) NRS. A weekly value will be calculated as long as at least one daily measure is recorded.

The primary ITT analysis will provide the following causal estimand for the primary analysis: the difference in the weekly mean change from Baseline of the daily patient self-reported 24-hour recall worst Long COVID pain intensity rating using an 11-point (0−10) NRS evaluated at the Week 14 endpoint in all randomized patients attributable to the initially randomized treatment assignment. The primary analysis will use a Mixed Model Repeated Measures (MMRM) approach with multiple imputation (MI) for missing data. Covariates in the model will include the fixed categorical effects of treatment, pooled site (with small sites pooled into a single large site), study week, and treatment by study week interaction, as well as the continuous fixed

covariates of baseline score and baseline score by study week interaction. Please see the separate Statistical Analysis Plan (SAP) for more details on the primary and secondary analyses and handling of missing data.

A hierarchical testing strategy will be applied to perform confirmatory analysis of the primary endpoint and key secondary efficacy endpoints; testing will begin with the first endpoint (primary endpoint) and continue through the sequence of key secondary endpoints only until an endpoint is not statistically significant. The order will be specified in the statistical analysis plan.

Safety Analyses:

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized overall and by preferred term and system organ class. AEs will also be summarized by severity and relationship to study drug. Serious AEs, AEs involving the oral cavity, and AEs leading to discontinuation of study drug will also be summarized. Actual values and changes from Baseline for clinical laboratory test results and vital signs will be summarized using descriptive statistics (n, mean, standard deviation, median, range, minimum, and maximum). The number of patients with Baseline and treatment-emergent suicidal ideation and/or suicidal behavior or self-injurious behavior, based on the C-SSRS, will be summarized by treatment group.

Sample Size:

The study is planned to enroll approximately 470 patients total in a 1:1 randomization; that is, 235 patients in each of the TNX-102 SL and placebo arms. Using a two-sided test with an alpha level of 0.05, a sample size of 235 per group provides a power of at least 90% if the effect size is 0.3.

Interim Analysis

An interim analysis will be completed when approximately 50% of the initially planned enrollment is evaluable for efficacy assessments. The analysis will be conducted for the purpose of potential sample size re-estimation, early stop for futility, and early stop for efficacy. This will be evaluated by an independent data monitoring committee; only recommendations on early stopping, continuing with the sample size as planned, or a sample size adjustment will be communicated to the Sponsor.

In the case of an early stop for efficacy, all ongoing patients will be asked to return to the clinic and complete an ET Visit, and the study will be halted once all patients have completed their termination visit.

Full details of the interim analysis will be included in the SAP and finalized prior to execution of the interim analysis.

Pharmacogenomic Analysis

Potential genetic determinants of treatment response will be examined by the assessment of genetic variants in relation to treatment outcome. Blood samples will be obtained from each

patient who provided separate written, signed informed consent form for pharmacogenomic analysis. These samples may be obtained at any post-screening visit, including an ET Visit; however, it is preferred that they are collected at Visit 2 whenever possible.

The pharmacogenomic analyses will involve whole genome sequencing (WGS) and analysis for allelic polymorphisms related to treatment response to TNX-102 SL. It is presumed that unused sample will be stored up to 15 years, and potentially utilized to develop a pharmacogenomic test for determining likelihood of treatment response to TNX-102 SL.

Table 2: Study Design and Schedule of Assessments

Assessment	Screening and Washout Period [a]	Diary Run-in Period	Baseline/ Randomization	Week 2 [u]	Week 6 [u]	Week 10 [u]	Week 14 / ET [b]	Week 16/ (Post-study Safety Follow-up) [v]	Week 18/ (1-Month Post-study Safety Follow-up) [w]
Study Day	**-35 to -1**	**-7 to -1**	**1**	**15 (-4 /+7)**	**43 ± 7**	**71 ± 7**	**99 (-4 /+7)**	**113 ± 7**	**127 ± 7**
Visit Number	**V1**		**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**
Informed consent	X								
In-/exclusion criteria	X								
Demographics	X								
Medical history	X		X [c]						
Confirmation of prior SARS-CoV-2 infection [x]	X								
WHO COVID-19 severity classification	X								
Prior/Concomitant medications	X		X [c]	X	X	X	X	X	X
Physical examination	X [d]		X [e]				X [e]		
Inspection of oral cavity [f]	X		X	X	X	X	X		
Modified Michigan Body Map (mMBM)	X [g]		X [h]	X [h]	X [h]	X [h]	X [h]		
MINI 7.0.2 Modules A, C, I, J, K, O (MDE, Bipolar, EtOH, Substance Use, Psychotic Disorders, Med/Organic/Drug-Related R/Os)	X								
MSI-BPD	X								
Columbia-Suicide Severity Rating Scale (C-SSRS)	X		X	X	X	X	X		
Sheehan Disability Scale [i]			X	X	X	X	X		
In-clinic assessment of Long COVID pain (7-day recall)	X [j]								
PROMIS – Sleep Disturbance [i]			X	X	X	X	X		
PROMIS – Fatigue [i]			X	X	X	X	X		
PROMIS – Cognitive Function – Abilities [i]			X	X	X	X	X		
Patients' Global Impression of Change (PGI-C) Assessment [i]				X	X	X	X		

Assessment	Screening and Washout Period [a]	Diary Run-in Period	Baseline/ Randomization	Week 2 [u]	Week 6 [u]	Week 10 [u]	Week 14 / ET [b]	Week 16/ (Post-study Safety Follow-up) [v]	Week 18/ (1-Month Post-study Safety Follow-up) [w]
Study Day	**-35 to -1**	**-7 to -1**	**1**	**15 (-4 /+7)**	**43 ± 7**	**71 ± 7**	**99 (-4 /+7)**	**113 ± 7**	**127 ± 7**
Visit Number	**V1**		**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**
Post-COVID-19 Functional Status (PCFS) scale	X		X				X		
Insomnia Severity Index (ISI)			X				X		
Epworth Sleepiness Scale (ESS) [i]			X	X	X	X	X		
Clinical laboratory tests [k]	X				X		X		
Viral laboratory testing [l]	X								
Drug screen	X [m]								
Serum pregnancy test [n] (processed by central lab)	X								
Urine pregnancy test [n] (processed in-clinic)			X	X	X	X	X		
Vital signs [o]	X		X	X	X	X	X		
12-lead electrocardiogram [p]	X								
Randomization criteria and procedures			X						
Patient training and eDiary review [q]	X		X	X	X	X	X		
eDiary assessment of 24-hour recall of worst Long COVID pain and sleep quality (daily) [r]	X	X	X	X	X	X	X		
Dispense double-blind study drug [s]			X	X	X	X			
Study drug compliance				X	X	X	X		
Pharmacogenomic blood draw (optional) [t]			*	*	*	*	*		
Adverse events			X	X	X	X	X	X	X
Assess diary compliance			X	X	X	X	X		

Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale; COVID-19 = Coronavirus diseas-19; ECG = electrocardiogram; ESS = Epworth Sleepiness Scale; ET = Early Termination; ISI = Insomnia Severity Index; mMBM = modified Michigan Body Map; MSI-BPD = McLean screening instrument for borderline personality disorder; PCFS = Post-COVID-19 Functional Status;; PGI-C = Patients' Global Impression of Change; PROMIS = Patient Reported Outcomes Measurement Information System; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; V = Visit; WHO = World Health Organization.

[a] Patients will be required to stop all excluded medications or begin down titration, if needed before discontinuation. Washout should be completed by Day -21 so there is a 14-day drug-free interval prior to the beginning of the collection of Baseline diary data that takes place during the 7 days leading up to

the Baseline/Randomization Visit. Patients will return for an unscheduled visit after the first 2 weeks of Washout have been completed; generally, this can be done at Day -8 or earlier.

[b] Patients who discontinue from the study before completing the Week 14 Visit will be asked to return to the site for an Early Termination (ET) Visit to have Week 14 assessments completed.

[c] Any additional (pre-screening) medical findings or medications discovered after the Screening Visit are to be noted in the medical history, Prior/Concomitant Medication Pages, respectively.

[d] A full physical examination, including measurement of height and weight and calculation of the body mass index, will be performed at Screening.

[e] A brief physical examination will be performed at Baseline and Week 14/ET. For patients for whom a telephone visit is being conducted for Week 14/ET, the brief physical exam will not be required.

[f] There will be a thorough examination (visual and palpation) of the oral cavity at the Screening Visit and then visual examinations at all other in-clinic visits. For visits at which a visual exam is not possible (ie, telephone visit), the visual oral cavity exam is not required; in lieu of the in-clinic (or home visit) oral cavity exam, after conclusion of "any changes in your medical condition", ask specifically if there have been any changes or problems in the oral cavity. Patients reporting any concerning lesion description or painful processes in the oral cavity possibly related to study drug exposure should be strongly urged to come into clinic for an Unscheduled Visit for oral cavity exam. In circumstances in which, due to the COVID-19 pandemic, it is not possible for the patient to return to the clinic for the Unscheduled Visit exam, a clinician certified by the Sponsor to conduct oral cavity examination should contact the patient by phone and obtain greater history and description of the oral cavity AE by patient, potentially augmented with images of oral cavity taken by the patient and sent to the site for the examining clinician to textually document in the source. In addition to the regularly scheduled in-clinic examinations, an unscheduled examination of the oral cavity in-clinic should be performed any time a patient contacts the clinic to report an oral cavity lesion or other oral AE possibly related to study drug exposure, other than oral numbness, tingling, or noticeable taste (eg, bitter, metallic, or unpleasant) after dosing, which do not require unscheduled examinations.

[g] The Screening version of the mMBM will be administered.

[h] The Baseline/Post-Randomization version of the mMBM will be administered.

[i] For telephone visits, the patient will be mailed all applicable patient reported outcomes for a given visit.

[j] Weekly recall of daily average Long COVID pain intensity on the NRS scale is required at the Screening Visit. Patients should only continue screening if they score ≥ 4 and ≤ 9.

[k] Clinical laboratory tests will be performed at Screening, Week 6, Week 14/ET. TSH, ESR, and HbA1c will be tested at Screening only.

[l] Human immunodeficiency virus (HIV), hepatitis C virus (HCV) and hepatitis B surface antigen (HBsAg) testing will be performed at Screening and may be performed at other visits, at the discretion of the Investigator or Sponsor. Medical Monitor approval is required for repeat testing.

[m] The urine drug screen is mandatory at Visit 1. If the screening urine drug screen (UDS) is positive for opioids, benzodiazepines, or amphetamines and washout is appropriate, the patient will need to return to the clinic for an unscheduled UDS prior to the beginning of the 7-day baseline data collection phase leading up to Visit 2. Opioid and stimulant retesting can be performed with an in-clinic UDS, whereas the UDS must be analyzed centrally in patients washing off of benzodiazepines. Urine drug screening may be repeated at the Investigator's discretion at any time.

[n] A serum pregnancy test will be performed at Screening, followed by in-clinic urine pregnancy tests at Baseline, Week 2, Week 6, Week 10, and Week 14/ET for women of child-bearing potential. For patients for whom a telephone visit is being conducted, the urine pregnancy test will be performed by the patient at home.

[o] Vital signs (oral temperature, sitting blood pressure and heart rate [obtained after resting for 5 minutes in a sitting position]) will be measured at each visit. For patients for whom a telephone visit is being conducted, the vital signs will not be required.

[p] A 12-lead electrocardiogram will be obtained at Screening. All electrocardiograms will be performed and interpreted locally.

[q] Clinic staff members will train the patient on how to take the study drug and how to complete an electronic diary (eDiary). In addition, patients will be asked to complete a brief training on accurate pain reporting and placebo response reduction training at each study visit. Patients will be asked to complete

their eDiary every evening. eDiary completion will start on the evening of Visit 1 and continue through Week 14. eDiary responses will be monitored during the study.

[r] Patients will assess their worst daily Long COVID pain over the last 24 hours every evening using an 11-point (0–10) numerical rating scale. Patients should be instructed to complete their diary responses in the evening, but before taking their bedtime dose of study drug. The 24-hour recall interval will assess the previous night's sleep and symptoms of pain since bedtime the previous night.

[s] The study drug will be dispensed to patients at Baseline on Day 1 (following randomization) and at Weeks 2, 6, and 10. One bottle will be dispensed on Day 1, and two bottles will be dispensed at Weeks 2, 6, and 10. For patients for whom a telephone visit is being conducted, the study drug will be mailed via courier to their home. Patients will be instructed to take 1 tablet of study drug sublingually every evening at bedtime for 2 weeks starting the evening of Day 1, and then 2 tablets sublingually every evening from Week 2 to Week 14.

[t] * The blood draw for the pharmacogenomic assessment can be obtained at any study visit post-Screening (including an ET Visit). Due to circumstances caused by the COVID-19 pandemic and the possibility of no further in-clinic visits after Baseline Visit (Visit 2), it is strongly recommended that the pharmacogenomics blood sample be obtained at the Baseline Visit (Visit 2). It should only be obtained one time during the study. Separate written, signed informed consent is required if the patient is to participate in the optional pharmacogenomic assessment.

[u] The Week 2, Week 6, and Week 10 Visits may be performed via telephone only when an in-clinic visit is not feasible due to the COVID-19 pandemic. Select safety assessments specifically required in-clinic will not be required for the telephone visits (eg, vital signs and oral cavity exam). Telephone visits for Week 14/ET Visits are to be strongly discouraged due to inability to obtain several safety measures (eg, vital signs, physical exam, oral cavity exam, chemistry and hematology labs), but telephone visits will be permitted for Week 14/ET Visit if attendance of an in-clinic visit is absolutely impossible or refused by the patient as a result of the COVID-19 pandemic and it is not feasible for the site to conduct a home visit.

[v] Visit 7 (Week 16 or approximately 2 weeks after ET) will be a telephone visit.

[w] Visit 8 (Week 18 or approximately 4 weeks after ET) will be a telephone visit.

[x] Confirmation of prior SARS-CoV-2 infection can be obtained through either a polymerase chain reaction (PCR) or nucleic acid tests or a rapid antigen test. Acceptable documentation of SARS-CoV-2 infection may be through either a laboratory report or formal documentation either generated at the point-of-care or by a virtual at-home test proctor/telehealth service.

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

LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Term	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BMI	body mass index
BUN	blood urea nitrogen
CBP	cyclobenzaprine HCl
CFR	Code of Federal Regulations
CFS	chronic fatigue syndrome
CGRP	calcitonin gene-related peptide
CI	confidence interval
CK	creatine kinase
COVID-19	Coronavirus Disease 2019 - viral illness caused by SARS-CoV-2
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP3A4	cytochrome P450 subtype 3A4
DDFM	denominator degrees of freedom
eg	*exempli gratia* (for example)
EC	ethics committee
ECG	electrocardiogram
ER	extended release
ESS	Epworth Sleepiness Scale
ET	Early Termination (ie, discontinuation from trial)
etc.	*et cetera* (and other things)
FDA	US Food and Drug Administration
FM	fibromyalgia
g	gram(s)
GCP	good clinical practice
GLP	good laboratory practice
h	hour(s)
HbA1c	glycated hemoglobin
HBsAg	hepatitis B surface antigen
HCl	hydrochloride
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ie	*id est* (that is)
ICF	informed consent form
ICH	International Council for Harmonisation

Term	Definition
IND	Investigational New Drug (application)
IR	immediate release
IRB	institutional review board
IRT	Interactive Response Technology
ISI	Insomnia Severity Index
ITT	intention-to-treat
kg	kilogram(s)
L	liter(s)
LOE	lack of efficacy
LS	least square (mean)
MAR	missing at random
MBM	Michigan Body Map
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCMC	Markov Chain Monte Carlo
MCV	mean corpuscular volume
MedDRA®	*Medical Dictionary for Regulatory Activities*®
mg	milligram(s)
MI	multiple imputation
min	minute(s)
MINI	Mini International Neuropsychiatric Interview
mL	milliliter(s)
mMBM	modified Michigan Body Map
MMRM	mixed-effects model repeated-measures
MNAR	missing not at random
msec	millisecond(s)
MSI-BPD	McLean Screening Instrument for BPD
N, n	number (of patients)
NA	not applicable
NDA	New Drug Application
ng	nanogram(s)
NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drug
PASC	post-acute Sequelae of SARS-CoV-2 Infection
PCFS	Post-COVID-19 Functional Status Scale
PCR	polymerase chain reaction
PGI-C	Patient Global Impression of Change
PI	Principal Investigator
PRO	patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
PTSD	post-traumatic stress disorder
QTcF	QT corrected for heart rate using Fridericia's formula
RBC	red blood cell

Term	Definition
R/O	Rule out
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2 – the virus that causes viral illness known as COVID-19
SAS	Statistical Analysis System
SDS	Sheehan Disability Scale
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SL	sublingual
SOC	system organ class
TEAE	treatment-emergent adverse event
TID	three times daily
THC	tetrahydrocannabinol
TNX-102 SL	cyclobenzaprine HCl sublingual tablets
TSH	thyroid-stimulating hormone
UDS	urine drug screen
US	United States
VHA	Veterans Health Administration
vs	versus
WBC	white blood cell
WHO	World Health Organization
WPI	Widespread Pain Index

5. INTRODUCTION

5.1. Overview of PASC

5.1.1. Definition and Characteristics

A set of symptoms experienced by people with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of Coronavirus Disease 2019 (COVID-19), with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis, has been termed Post-acute Sequelae of SARS-CoV-2 infection (PASC) (colloquially known as "Long COVID" or "long haulers"). Common symptoms include fatigue, shortness of breath, and cognitive dysfunction, as well as others that generally have an impact on everyday functioning. Symptoms may be new onset, following initial recovery from an acute COVID-19 episode, or persist from the initial illness. Symptoms may also fluctuate or relapse over time (World Health Organization; WHO 2021).

The lack of a standardized definition for PASC makes it difficult to determine the exact epidemiology, incidence rates, and the impact of the condition on long-term disability. A conservative estimate based on data collected from numerous countries is that, on average, 30% (range 32.6% to 87.4%) of people with COVID-19 experience PASC (summarized in Nalbandian et al. 2021).

The WHO-endorsed definition states that PASC occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Therefore, PASC can broadly be described as the presence of one or more symptoms (continuous or relapsing/remitting; new or same symptoms of acute COVID-19) in individuals who have been infected with SARS-CoV-2 after the expected period of clinical recovery (Raveendran et al. 2021).

Symptoms of PASC have been variably reported as including fatigue, muscle weakness, diaphoresis, myalgia, arthralgia, chills, limb edema, dizziness, post-exertional malaise, cognitive dysfunction, respiratory symptoms (polypnea, chest pain, cough, sputum, sore throat), cardiovascular abnormalities, alopecia, olfactory abnormalities, psychosocial symptoms (such as sleep difficulties, depression, anxiety, feelings of inferiority), and generally a worse quality of life (Gagnier et al. Submitted; Davis et al. 2021; Lambert et al 2021; Bierle et al. 2021; Crook et al. 2021; Raveendran et al. 2021).

Fatigue is the most common symptom reported in PASC patients, occurring in roughly 40% to 80% of patients at an average of 4 to 8 weeks post-onset (Crook et al. 2021; Davis et al. 2021; Lambert et al 2021; Lopez-Leon et al. 2021; Bierle et al. 2021). In a telephone study performed in the United States (US), of 488 patients, 32.6% reported persistent symptoms at 60 days post-discharge from the hospital, including 18.9% with new or worsened symptoms (Chopra et al. 2020). Fatigue has been reported in 77.7% of those with symptoms at 6 months post-infection, according to a survey disseminated via email, social media, and online patient support groups (Davis et al. 2021).

Muscle pains and aches were reported in 43.7% of those with symptoms at 6 months post-infection (Davis et al. 2021). The authors noted that PASC features involving pain occurred more

commonly than any of the other features (34.2%), and occurred more commonly than after influenza (24.0%). Also, pain was the only feature that had a higher incidence in the 3- to 6-month period than in the 0- to 3-month period. The authors conclude that pain appears to be a prominent and relatively persistent element of PASC (Taquet et al. 2021).

Clauw and colleagues from University of Michigan are currently conducting a study to: (1) understand the experience of PASC among those who are Black or African American; and (2) identify factors that support or hinder their ability to manage and cope with PASC symptoms. Data are collected using semi-structured interviews that are visually and/or audio recorded. Of those who have participated in the study thus far, a third have reported pain symptoms. Some patients reported swelling and pain in joints, either as an exacerbation of previous pain or as new pain. The interviews revealed that the pain manifests mostly as headaches/facial pain, back pain, and joint pain and that it is either persistent or occurs in relapsing episodes. The pain was associated with significant distress, functional impairments, and decrease in quality of life (Clauw et al. Data on File/ Personal Communication).

A variety of sleep disturbances have also been reported in PASC. In one report, nearly 80% of PASC patients experienced sleep disturbances, including insomnia, difficulty falling asleep, vivid/lucid dreams, and nonrestorative sleep (Davis et al. 2021).

Al-Aly and colleagues reported on the burden of PASC in a large cohort that included 73,435 users of the Veterans Health Administration (VHA) with COVID-19 who survived for at least the first 30 days after their COVID-19 diagnosis and who were not hospitalized vs nearly 5 million VHA users who were hospitalized but not for COVID-19. Individuals with COVID-19 exhibited an excess burden of poor general well-being, including sleep-wake disorders (hazard ratio 14.53 [confidence interval (CI) 11.53−17.36]), malaise and fatigue (12.64 [11.24–13.93]), musculoskeletal pain (13.89 [9.89−17.71]), muscle disorders (5.73 [4.60–6.74]), and arthralgia and arthritis (5.16 [3.18–7.01]) (Al-Aly et al. 2021).

Therefore, PASC symptoms span multiple organ systems and may have significant effects on physical and mental health, functional status, and quality of life.

5.1.2. PASC and Fibromyalgia

Among the symptoms that characterize PASC, multi-site pain, sleep disturbances, and fatigue have been reported in several longitudinal studies of PASC (Lambert et al 2021; Davis et al. 2021; Bierle et al. 2021). This has prompted several groups to propose that PASC may be a condition similar to other central sensitization/nociplastic pain syndromes, such as fibromyalgia (FM), chronic fatigue syndrome (CFS), or postural orthostatic tachycardia syndrome (Bierle et al. 2021; Ursini et al. 2021; Clauw et al. 2020).

Multi-site pain in association with fatigue and cognitive and sleep disturbances, such as observed in patients with PASC, is a characteristic feature of FM (Mease et al. 2009). Pain associated with FM and other complex regional pain syndromes are generally independent of underlying tissue damage and are believed to reflect abnormalities of central pain perception (Fitzcharles et al. 2021; Minhas et al. 2021; Kosek et al. 2021).

A connection between PASC and FM has been proposed by other groups. Based on their analysis of patient appointment request documentation for 465 people with confirmed or suspected

COVID-19 infection, Bierle and colleagues identified a subset of 42 (9%) patients who met criteria for a significant post-viral syndrome with central sensitization, which they termed Post-COVID Syndrome (PoCoS). Furthermore, they proposed that, if these symptoms persist past 6 months, these patients may meet the clinical definition of one of the central sensitization syndrome disorders, such as FM, CFS, or postural orthostatic tachycardia syndrome (Bierle et al. 2021).

In a web-based survey distributed through social networks, Ursini and colleagues collected information from people who have had COVID-19 diagnosis 6 ± 3 months earlier using the American College of Rheumatology 2010 FM Survey Criteria modified for self-administration. They found that, of the 616 responders, 189 (30.7%) met the criteria for FM after an average of 6 months since COVID-19 diagnosis (Ursini et al. 2021).

We hypothesize that chronic multi-site pain reported in PASC patients involves pathophysiological mechanisms similar to those of FM and nociplastic pain (Clauw et al. 2020; Bierle et al. 2021; Ursini et al. 2021; Fitzcharles et al. 2021; Minhas et al. 2021; Kosek et al. 2021) and will therefore respond to treatments that are effective in FM.

5.2. Background of TNX-102 SL

TNX-102 SL (cyclobenzaprine HCl sublingual tablets) is being developed through 505(b)(2) New Drug Applications (NDAs) for FM, post-traumatic stress disorder (PTSD), Agitation in Alzheimer's Disease, and Alcohol Use Disorder using AMRIX (extended release [ER] capsule, 30 mg; AMRIX® Prescribing Information, 2019) as the reference listed drug. We are currently also developing TNX-102 SL for the treatment of multi-site pain in PASC.

The TNX-102 SL is a formulation containing 2.8 mg cyclobenzaprine HCl [3-(5H-dibenzo[a,d]cycloheptene-5-ylidene)-N,N-dimethyl-1-propanamine hydrochloride] for sublingual (SL) administration. The active ingredient in TNX-102 SL, cyclobenzaprine HCl (CBP), has been approved for use in the US since 1977, originally as FLEXERIL® 10-mg oral tablets indicated as an adjunct to rest and physical therapy for the relief of muscle spasm associated with acute, painful musculoskeletal conditions. The usual dose for this indication is 30 mg or 15 mg per day taken as 10 mg three times daily (TID) or 5 mg TID, respectively (FLEXERIL® Prescribing Information, 2013). The FLEXERIL® brand of immediate-release (IR) CBP tablets was discontinued in May 2013. Generic CBP is available and marketed in a variety of strengths, including 5-, 7.5- and 10-mg IR tablets. AMRIX® (AMRIX® Prescribing Information, 2019), an ER capsule of CBP, was approved in 2007 in the US through an NDA and is currently available in 15 and 30 mg, taken once a day for the same indication as FLEXERIL® in the US. Both FLEXERIL® and AMRIX® are indicated for 2–3 weeks use only. No CBP product has been approved for use in PASC by the Food and Drug Administration (FDA), Health Canada, or in any other country.

In addition to its therapeutic effects on muscle spasm, CBP also exhibits functional antagonism of 5 HT2A, α1-adrenergic, H1-histaminergic, and M1-muscarinic acetylcholine receptors, and these actions may underlie its putative ability to improve sleep quality. TNX-102 SL is a low-dose sublingual formulation of CBP being developed to provide greater diurnal variation in peak-to-trough drug levels to enhance nocturnal treatment effects while minimizing daytime side effects.

TNX-102 SL is a non-opioid centrally-acting analgesic that is hypothesized to have activity that is mediated by targeting sleep disturbances. Prior studies performed in FM patients and PTSD patients saw that improvement in sleep precede and predict improvements of global symptoms of these disorders. Thus, given that difficulty sleeping and chronic pain are common symptoms of PASC, the proposed treatment with TNX-102 SL 5.6 mg taken daily at bedtime may provide adequate relief of PASC symptoms by promoting improvement in sleep quality, and, secondarily, improvement in chronic pain, fatigue, anxiety and mood, and cognitive function.

5.3. Scientific Rationale

The symptoms of PASC can roughly be divided into 4 groups, including: 1) direct organ or tissue damage due to the acute infection, 2) COVID-19-induced hypercoagulable states, 3) mental health issues triggered by the infection, isolation, and disparities in health, and 4) a set of non-specific symptoms including multi-site pain, sleep disturbances, and fatigue (Lopez-Leon et al. 2021; Sudre et al. 2021; Huang et al. 2021; Clauw et al. 2020). The development program for TNX-102 SL (cyclobenzaprine HCl sublingual tablets) is aimed at palliation of this latter mechanism, focusing on identifying and treating individuals with multi-site pain due to PASC who display the primary symptoms observed in common overlapping pain conditions, such as FM, CFS, tension headache, irritable bowel syndrome, and bladder pain syndrome (Fitzcharles et al. 2021; Kosek et al. 2021; Larkin et al. 2021; Kratz et al. 2021).

5.3.1. Case Definition of Multi-Site Pain Associated with PASC

We define multi-site pain as chronic pain in 4 or more regions on the modified Michigan Body Map (mMBM; Appendix 2), a self-report measure to assess body areas of chronic pain. The original Michigan Body Map is depicted in Figure 1.

In a series of studies using lower extremity arthroplasty as a model for pain originating in the periphery (which should be relieved with surgery), Dr. Daniel Clauw from the University of Michigan and his colleagues showed that, for each 1-point increase in the 2016 FM Survey criteria, there was a 25% decrease in response to surgery intended to relieve pain (Brummett et al. 2015a), and, similarly, non-responsiveness to opioids (Goesling et al. 2016). In order to identify a data-driven cut-off point for multi-site pain, they analyzed the data from Brummett et al. 2015a specifically comparing the number of pain regions (out of a possible 7, including left arm, right arm, left leg, right leg, front of trunk, back of trunk, and head) to the incidence of the other key features of pain in central sensitization (memory and sleep problems, fatigue, decreased functional status). They measured the participants' ability to perform tasks (per PROMIS Physical Function Scale) scored on a numeric scale from 1 to 5 (see Figure 2 footnote for details). Before surgery (Figure 2A), the average score of ≥ 3 ("with some difficulty") for the functional status measures was observed independent of the number of pain sites. Six months after the surgery (Figure 2B), the average scores for only those participants with ≥ 4 pain sites indicated at least "a little difficulty" with performing tasks (score of ≥ 2). Furthermore, they observed an increase in the co-morbid non-pain symptoms, such as fatigue, sleep, memory and cognitive function, as the number of regions affected by pain increased from 3 to 4 (Clauw et al. Data on file/Personal communication).

The MBM has been used to assess widespread pain in a number of recent studies (Brummett et al. 2013a; Brummett et al. 2013b; Brummett et al. 2015a; Brummett et al. 2015b; Hassett et al.

2012; Hassett et al. 2013; Janda et al. 2015; Wasserman et al. 2014). Based on the studies of Clauw et al, multi-site pain, defined as pain persisting in 4 or more regions on the mMBM, would be indicative of the widespread pain associated with PASC.

Figure 1: Michigan Body Map

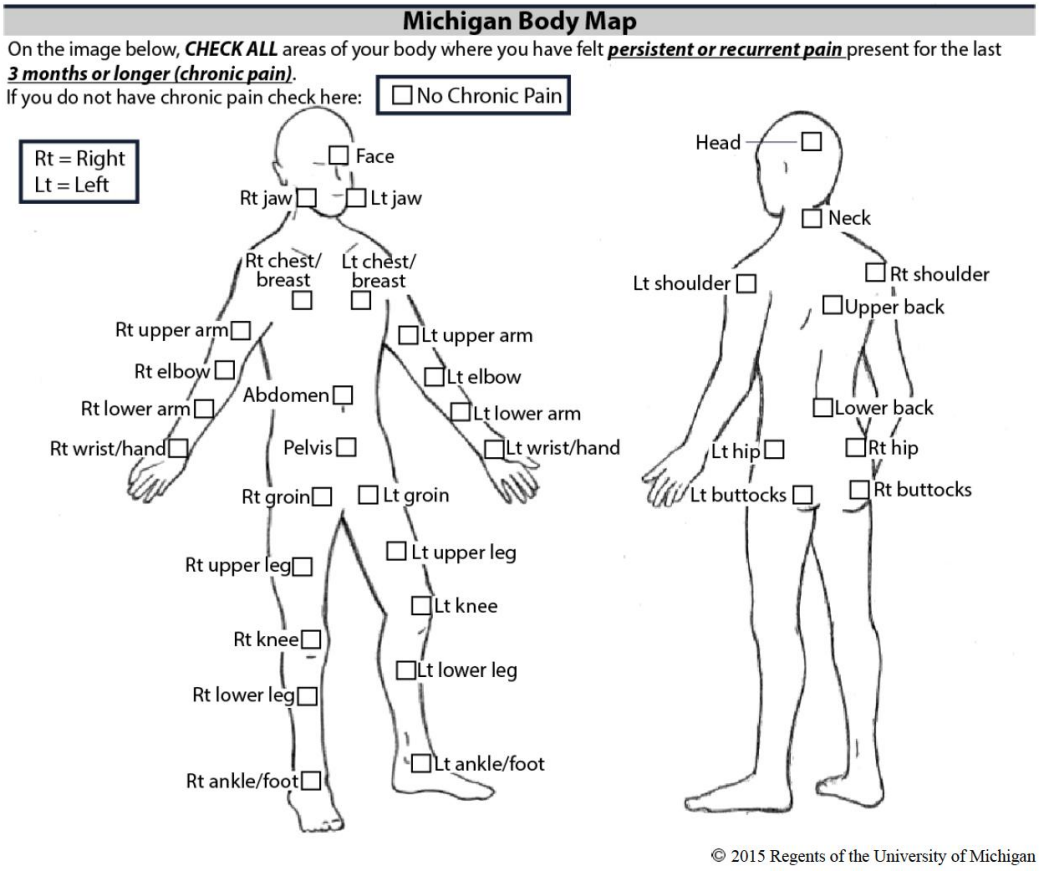
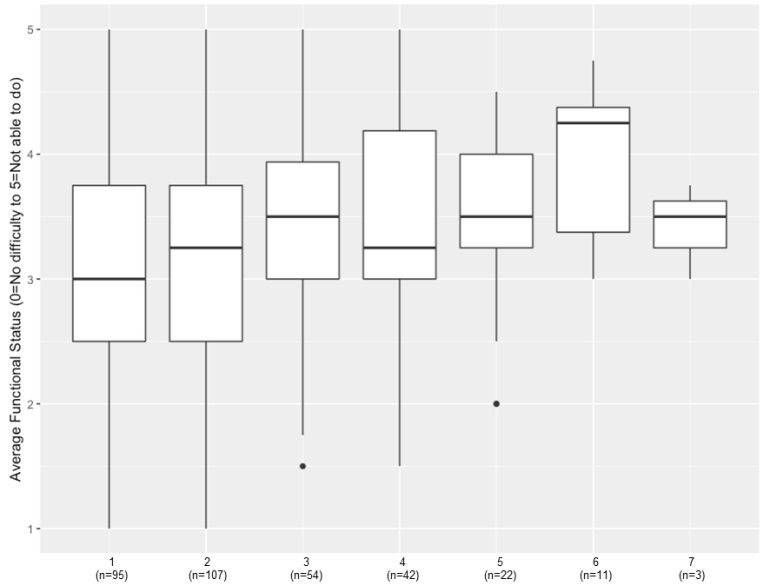
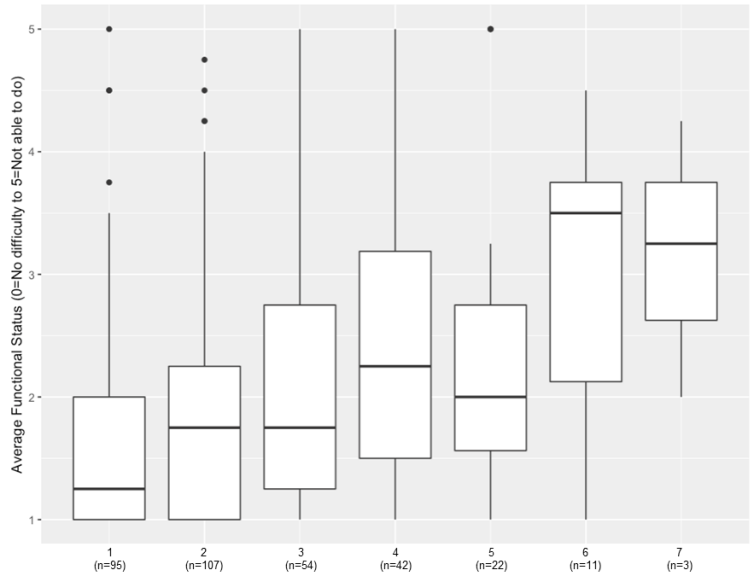


Figure 2: Functional Status* of Patients Undergoing Arthroplasty by Number of Pain Sites at Baseline

A. Before surgery



B. Six months after surgery



N = 334.
Data are medians and interquartile ranges.
* Functional status measures on a 4-Item PROMIS Physical Function Scale:
PFA11 = Are you able to do chores such as vacuuming?
PFA21 = Are you able to go up and down the stairs at a normal pace?
PFA23 = Are you able to go for a walk for at least 15 min?
PFA53 = Are you able to run errands and shop?
1= without any difficulty, 2= with a little difficulty, 3= with some difficulty, 4= with much difficulty, 5= unable to do.

PF = [PROMIS] Physical Function [scale].

5.3.2. TNX-102 SL in the Treatment of Fibromyalgia

One Phase 2 and two Phase 3 studies evaluated TNX-102 SL in patients with FM. Even though the Phase 2 study and the first Phase 3 study (TNX-CY-F301), both using 2.8 mg dose of TNX-102 SL, narrowly missed on their primary pain efficacy endpoint, both studies showed significant improvements in FM pain when analyzed by other standard statistical approaches, as well as significant improvements in sleep quality, Patient Global Impression of Change, and fibromyalgia-specific measures.

Based on these promising results, the next Phase 3 study (TNX-CY-F304/F304) in FM used TNX-102 SL at the 5.6 mg dose. In this 14-week randomized, double-blind, placebo-controlled, multicenter Phase 3 study, 503 patients were randomized to receive either TNX-102 SL or placebo. For the first 2 weeks of treatment, patients started on TNX-102 SL 2.8 mg (1 tablet) or placebo. Starting at the Week 2, all patients had the dose increased to TNX-102 SL 5.6 mg (2 x 2.8 mg tablets) or 2 placebo tablets for 12 weeks of treatment. The study showed a reduction in the weekly average daily diary pain scores at Week 14 (primary endpoint). The treatment group difference (TNX-102 SL minus placebo) in daily pain reduction was statistically significant (p=0.010) in favor of TNX-102 SL. The primary efficacy analysis was also supported by an exploratory 30% responder analysis of daily diary pain (p=0.006). A second Phase 3 study (TNX-CY-F306/F306) with a similar design discontinued enrollment after an interim analysis when an independent data monitoring committee recommended to stop the study early for futility. The study did not achieve statistical significance on the primary endpoint in the weekly average daily diary pain scores at Week 14 (p=0.115), which Tonix believes was due to an unexpected higher rate of adverse-related discontinuations in both the active and placebo groups compared to prior studies of TNX-102 SL. However, there was strong activity on sleep disturbance (p=0.004) and on the Patient Global Impression of Change (p=0.038). Encouraged by these results, a third potential pivotal Phase 3 study in FM with a similar design is currently ongoing.

In the studies in FM patients, the improvement in pain can be assessed by the mean change from Baseline to Week 14 in a score based on the self-reported 24-hour recall of average pain intensity using an 11-point (0–10) numeric rating scale (NRS). As in these studies, multi-site pain was reproducibly measured using the pain NRS diary, we intend to measure effects of TNX-102 SL on pain in PASC patients as measured by the NRS diary.

5.4. Rationale for Dose Selection

Previous FM Phase 2 studies and the first Phase 3 study (TNX-CY-F301) used TNX-102 SL at the 2.8 mg dose. Although the study did not reach statistical significance for the primary endpoint of 30% responder analysis in pain (p=0.095), most secondary endpoints, including many other common statistical analyses of pain and sleep, were nominally significant. The second Phase 3 study of TNX-102 SL, TNX-CY-F302, was initiated in the first half of 2016 but was terminated upon receipt of the negative TNX-CY-F301 study primary analysis results. The findings from early Phase 2 and 3 studies used TNX-102 SL at the 2.8 mg dose provided an opportunity to reassess the optimal dose of TNX-102 SL and the most appropriate study design for the subsequent Phase 3 study in FM, TNX-CY-F304.

To evaluate whether the efficacy of TNX-102 SL on FM pain might be greater with a dose higher than 2.8 mg, in-clinic pain data from the Phase 2 study (TNX-CY-P201) in patients with PTSD were analyzed. Study TNX-CY-P201 was more restrictive than TNX-CY-F301 in terms of allowable pharmacological pain therapies, with exclusion of opiates, all antidepressants, and other pain treatments (eg, gabapentin, pregabalin). Like TNX-CY-F301, TNX-CY-P201 allowed only use of acetaminophen or NSAIDs for pain control. The TNX-CY-P201 subgroup included in this analysis consisted of patients with Baseline NRS scores of ≥ 4 for in-clinic assessments of average pain over the previous 24 hours, similar to the pain diary minimal pain requirement for randomization in the FM studies. Results showed that the TNX-102 SL 5.6 mg subgroup had the largest numerical improvement in pain scores at each post-baseline assessment (average difference from placebo in least squares mean change from Baseline across Weeks 2 through 12 was -0.81 units), whereas the TNX-102 SL 2.8 mg subgroup was similar to placebo. Numbers of patients in each group were too small for appropriate power to show statistical significance of 5.6 mg compared with placebo, but calculated effect sizes supported the effects of this dose on pain. The Cohen's D effect size after 12 weeks of treatment for TNX-102 SL 5.6 mg over placebo was 0.34, which is a clinically meaningful reduction in pain and on par with the effect sizes on pain of the 3 FDA-approved pharmacotherapies for FM (Perrot and Russell. 2014). These results of improved analgesic response while maintaining good tolerability in PTSD at 5.6 mg supported the notion that increasing the dose studied in FM may have a greater analgesic response on FM pain while maintaining an acceptable level of tolerability.

A 5.6-mg dose of TNX-102 SL was used in the Phase 3 study F304. In Study F304, the primary efficacy endpoint was the change from Baseline to Week 14 in the NRS weekly average of daily self-reported average pain intensity scores. The treatment group difference (TNX-102 SL minus placebo) in pain reduction was statistically significant (p=0.010) in favor of TNX-102 SL.

Given the overlapping symptoms of pain reported in FM and PASC, we believe that TNX-102 SL 5.6 mg is a promising first-line therapy to treat the proposed indication of multi-site pain associated with PASC.

5.5. Conclusion

We propose that PASC, characterized by a triad of multi-site pain, fatigue, and sleep disturbance, has features of central sensitization syndromes similar to FM. We propose to investigate the efficacy and safety of TNX-102 SL, which has shown promising results in treating FM, as a treatment of multi-site pain in patients with PASC.

6. TRIAL OBJECTIVES

6.1. Primary Objective

To evaluate the efficacy of TNX-102 SL 5.6 mg daily at bedtime in the treatment of patients with multi-site pain associated with Long COVID.

6.2. Secondary Objective

To evaluate the safety and tolerability of TNX-102 SL 5.6 mg daily at bedtime in the treatment of multi-site pain associated with Long COVID.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a Phase 2, randomized, parallel-group, double-blind, placebo-controlled, 14-week study designed to evaluate the efficacy and safety of TNX-102 SL 5.6 mg (2 x 2.8 mg tablets) taken once daily at bedtime for the management of multi-site pain associated with Long COVID. The study is to be conducted at approximately 30 investigational sites in the US.

The study will consist of a Screening Visit (Visit 1, Days -35 to -8), a Washout and Screening period of at least 7 days (for those patients not requiring washout) and no more than 35 days, inclusive of a 7-day baseline data collection phase immediately preceding the Baseline Visit. Eligible patients who provide written informed consent will have study assessments performed at Screening. Due to limitations in the diary completion window, patients who are planning on international travel during the study period should not be considered for the study. Patients whose employment involves overnight shifts also should not be considered for the study due to the restricted completion window and the requirement for consistent bedtime dosing.

At Screening Visit 1 and after signing the written informed consent, any required washout should be discussed with the patient and plans made for an appropriate schedule for reducing/stopping any excluded medications. This down-titration and discontinuation of excluded medications must be accomplished so that the patient is free of excluded medications for at least 14 days prior to beginning of the collection of Baseline diary data that takes place during the 7 days leading up to the Baseline/Randomization Visit. Any additional time required for down-titration would be in addition to this washout requirement. For extenuating circumstances, the total duration of the Screening period may be increased to up to a maximum of 49 days with Medical Monitor approval. All excluded medications will be stopped during the Washout period through the Week 14/ Early Termination (ET) Visit (Visit 6).

Patients will be trained on use of an eDiary system at Visit 1.

During the 7-day run-in Phase (7 days immediately preceding Visit 2 [Baseline/Randomization Visit; Day 1]) patients will be asked to record their worst daily Long COVID pain intensity on the 11-point (0−10) NRS scale using 24-hour recall and assess sleep quality from the previous evening, also using an 11-point NRS scale. The average of the 7 days immediately preceding Visit 2 (Baseline Randomization Visit; Day 1) will serve as the Baseline pre-treatment scores.

After completing any required washout of excluded therapies and recording Baseline Diary scores for at least 7 days, patients will return to the investigative site for Baseline assessments and randomization (Day 1, Visit 2), when they will be randomly assigned to receive TNX-102 SL or matching placebo sublingual tablets in a 1:1 ratio.

During the treatment phase, each evening, the system will prompt the patient to reflect on the past 24 hours and record their worst pain intensity, assess their sleep quality from the previous evening, and log study drug dosing from the previous night (post-randomization).

Patients will take the study drug SL once daily at bedtime, starting on the day of randomization (Day 1), for 14 weeks. For the first 2 weeks of treatment, patients will start on TNX-102 SL 2.8 mg/day (1 tablet) or placebo. Patients will continue to record their worst daily pain, assess their sleep quality from the previous evening, and log study drug compliance.

All patients will then return to the clinic at Week 2 (Visit 3) for efficacy and safety assessments and assessment of study drug compliance. The study drug dose will be increased to 2 tablets (5.6 mg; 2 x 2.8 mg TNX-102 SL tablets or placebo) or 2 placebo tablets taken SL and simultaneously daily at bedtime. Patients will next return to the clinic at Week 6 (Visit 4) for assessment of safety, efficacy, study drug compliance, and dose tolerability at the 5.6-mg dose. In scenarios in which TNX-102 SL 5.6 mg (or 2 placebo tablets) is considered intolerable due to adverse event(s) (AEs) and would otherwise lead to study discontinuation, with Medical Monitor approval, the Investigator may lower the daily dose to 1 tablet every night (TNX-102 SL 2.8 mg or 1 placebo tablet). If/when it is deemed clinically warranted by the Investigator, rechallenge with 2 tablets TNX-102 SL 2.8 mg (5.6 mg dose)/placebo may be attempted or the patient may remain on the lower dose for the remainder of the study. It will be emphasized to Investigators that such dosage reduction should only be considered when the patient's intolerability is sufficient to cause the patient to consider discontinuing from the study. It will be emphasized to participating patients that they should only make changes in study drug dose upon consultation with the Investigator, and they should notify the clinic immediately if they think the dosage needs to be adjusted. Ideally, any changes in dose should only be made at a scheduled visit, but, if it necessary to change dose between visits, the change should only be made upon the recommendation of the Investigator after discussion between the patient and the Investigator.

Patients will return to the clinic for safety, tolerability, and efficacy assessments, and assessments of study drug compliance at Week 2 (Visit 3), Week 6 (Visit 4), Weeks 10 (Visit 5) and 14 (Visit 6) or ET.

Approximately 2 weeks after Week 14 (Visit 6), there will be a Post-study Safety Follow-up telephone call (Visit 7), and approximately 4 weeks after Week 14, there will be a 1-Month Post-study Safety Follow-up telephone call (Visit 8).

Due to the exceptional circumstances caused by the COVID-19 pandemic, an option for a telephone visit will be available for Weeks 2, 6, 10 (Visits 3, 4, 5), and, only with Medical Monitor approval, Week 14/Visit 6 (or ET) for those unable to attend an in-clinic visit due to the COVID-19 pandemic. However, all visits should be conducted in person whenever possible.

The total duration of the study, including screening and follow-up, may be as long as 25 weeks. The maximum treatment duration will be 14 weeks.

Patients who wish to withdraw from the study may do so at any time.

The study timeline and events schedule are provided in Table 2.

7.2. Study Endpoints

7.2.1. Primary Efficacy Endpoint

- Change from Baseline in the diary NRS weekly average of daily self-reported worst Long COVID pain intensity scores at the Week 14 endpoint

7.2.2. Secondary Efficacy Endpoints

Key Secondary efficacy endpoints:

- Change from Baseline in the weekly average of the daily diary NRS assessment of sleep quality at the Week 14 endpoint
- Change from Baseline in the PROMIS score for fatigue at the Week 14 endpoint
- Change from Baseline in the PROMIS score for cognitive function at the Week 14 endpoint

Secondary Efficacy endpoints:

- Change from Baseline in the Patient Reported Outcomes Measurement Information System (PROMIS) score for sleep disturbance at the Week 14 endpoint
- Proportion of patients with a Patient Global Impression of Change (PGI-C) rating of "very much improved" or "much improved" at the Week 14 endpoint
- Change from Baseline to Week 14 in the Sheehan Disability Scale (SDS)
- Change from Baseline to Week 14 in the Insomnia Severity Index (ISI)
- Change from Baseline to Week 14 in the Epworth Sleepiness Scale (ESS)

7.2.3. Exploratory Efficacy Endpoints

- Proportion of patients with a ≥ 30% improvement from Baseline to Weeks 1−14 in the daily self-reported worst Long COVID pain intensity score
- Proportion of patients with a ≥ 50% improvement from Baseline to Weeks 1−14 in the daily self-reported worst Long COVID pain intensity scores
- Proportion of Patients with a PGI-C rating of "very much improved" or "much improved" at each post-randomization clinic visit
- PGI-C (1-7) rating at each post-randomization clinic visit
- Change from Baseline in the PROMIS score for sleep disturbance at each post--randomization clinic visit
- Change from Baseline in the PROMIS score for fatigue at each post-randomization clinic visit
- Change from Baseline in the PROMIS fatigue symptom questions 1,3,4 (individually and summed) at each post-randomization clinic visit
- Change from Baseline in the PROMIS fatigue impact questions 6,7,8 (individually and summed) at each post-randomization clinic visit
- Change from Baseline in the PROMIS score for cognitive function at each post--randomization clinic visit

- Change from Baseline in the weekly average of the daily diary assessment of sleep quality at Weeks 1−14
- Change from Baseline in the weekly average of the daily diary assessment of worst pain intensity scores at Weeks 1−14
- Change from Baseline in laboratory markers of inflammation
- Change from Baseline to Week 14 in the Post-COVID-19 Functional Status Scale (PCFS)
- Change from Baseline in the total number of the modified Michigan Body Map pain regions identified as having pain at each post-randomization clinic visit
- Change from Baseline in average NRS Long COVID pain intensity across the 7 pain regions in the modified Michigan Body Map at each post-randomization visit; regions without pain identified will be assigned a value of 0
- Change from Baseline in average NRS Long COVID pain intensity within the index site region on the modified Michigan Body Map at each post-randomization visit
- Change from Baseline in average NRS Long COVID pain intensity within the worst region for a given visit on the modified Michigan Body Map at each post-randomization visit; this will compare the value for the worst region at a visit and the worst region at baseline
- Subgroup analyses of the above endpoints by severity of their SARS-CoV-2 infection using groupings of the WHO ordinal scale of COVID severity as data allow
- Subgroup analyses of the above endpoints by COVID vaccine status

7.2.4. Safety

- Incidence of AEs
- Changes from Baseline in clinical laboratory tests
- Changes from Baseline in vital signs
- Assessment of physical examination findings, including examinations of the oral cavity
- Monitoring suicidality using Columbia-Suicide Severity Rating Scale (C-SSRS)

7.3. Number of Patients and Treatment Assignment

Approximately 470 patients (235 per arm) will be randomized in a 1:1 ratio to treatment with TNX-102 SL or placebo tablets. Randomized patients who withdraw will not be replaced.

8. SELECTION AND WITHDRAWAL OF PATIENTS

8.1. Informed Consent

A potential patient may be screened for eligibility only after the nature of the study, its purpose, and any other information relevant to the patient's decision to participate have been explained to him or her and the patient has voluntarily confirmed his or her willingness to participate. Informed consent is documented by means of a written, signed, and dated informed consent form (ICF). Additional information is provided in Section 16.3.

8.2. Patient Inclusion Criteria

Patients enrolled in this study will be volunteer patients. Eligible patients must meet all of the following inclusion criteria, as assessed at Screening Visit 1:

1. The patient is male or female, 18 to 65 years of age, inclusive.
2. The patient has a confirmed history of SARS-CoV-2 infection at least 3 months prior to enrollment, based on a documented written positive viral test at the time of active infection through either a polymerase chain reaction (PCR) or nucleic acid tests or a rapid antigen test. Acceptable documentation of SARS-CoV-2 infection may be through either a laboratory report or formal documentation either generated at the point-of-care or by a virtual at-home test proctor/telehealth service.
3. The patient has a history of COVID-19 infection with a grading of 1 to 6 on the World Health Organization (WHO) COVID-19 8-Category Ordinal Scale of Disease Severity (Appendix 1).
4. The patient has new onset or significant worsening of pain that coincides with a prior COVID-19 infection. The new or worsening pain following COVID-19 infection has been generally present for at least 3 months post initial COVID-19 diagnosis, but no longer than 18 months post initial COVID-19 diagnosis.
5. The patient meets criteria for multi-site pain as defined by the mMBM closely following the SARS-CoV-2 infection, which includes:
    - Multi-site pain, defined as pain in at least 4 out of 7 body regions (mMBM Part 2, Appendix 2).
6. The patient's in-clinic 7-day recall NRS average daily Long COVID pain intensity score at Screening Visit must be ≥ 4 and ≤ 9 (Appendix 3). Exceptions are only possible with Medical Monitor's approval.
7. The patient has a PCFS score of ≥ 2 (Appendix 4) at Screening and Baseline.
8. The patient does not have another disorder that would otherwise explain his/her pain.
9. If female, is either not of childbearing potential (defined as postmenopausal for at least 1 year or surgically sterile [eg, bilateral oophorectomy or hysterectomy]) or will be practicing one of the following methods of birth control throughout the study and for 28 days after study drug discontinuation:

a. Hormonal methods such as oral, implantable, injectable, or transdermal contraceptives for a minimum of one full cycle (based on the patient's usual menstrual cycle period) before study drug administration;
b. Intrauterine device;
c. Bilateral tubal ligation
d. Double-barrier method (condoms, sponge, diaphragm, or vaginal ring with spermicidal jelly or cream);
e. Partners of vasectomized males in stable relationships;
f. Females involved in same sex relationships;
g. Female patients practicing abstinence may have the birth control requirement waived only with Medical Monitor approval.

10. If the patient is vaccinated against the SARS-CoV-2 virus, the patient is at least 2 weeks past a vaccine dose.
11. If the patient is currently receiving any non-exclusionary pharmacologic treatments, the patient should be on stable doses of their treatment regimen for at least 4 weeks (except for allowed antidepressants, which require 90 days at stable dose) prior to randomization and should not be expecting dosing change during the period of the trial.
12. The patient must be willing and able to withdraw from the following therapies for the duration of the study: duloxetine, milnacipran, pregabalin, gabapentin, tramadol, tapentadol, amitriptyline and other tricyclic antidepressants, trazodone, narcotics/opioids, naltrexone (including CONTRAVE®), orexin receptor antagonists, all other forms of cyclobenzaprine (AMRIX®, or generic equivalents), and benzodiazepines.
13. The patient is willing and able to comply with all protocol-specified requirements.
14. The patient is capable of reading and understanding English and has provided written informed consent to participate.

8.3. Patient Exclusion Criteria

Patients who meet any of the following criteria as assessed at Screening Visit 1, should be excluded from the study:

1. The patient has been diagnosed with infectious or inflammatory arthritis (eg, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis), systemic lupus erythematosus, gout, or meets criteria for another type of systemic autoimmune disease (eg, Sjogren's disease).
2. The patient has been diagnosed with a complex regional pain syndrome, fibromyalgia, failed back surgery syndrome, persistent or prevalent pain symptoms related to systemic disease (eg, diabetic peripheral neuropathy, post-herpetic neuropathy), untreated hyperparathyroidism, or a history of prior surgery, trauma, organ or tissue damage, or other source of pain that, in the Investigator's opinion, would confound or interfere with the assessment of the patient's symptoms or require excluded therapies during the patient's study participation.

3. The patient has any lifetime history of bipolar disorder, schizophrenia, schizoaffective disorder, or other psychotic disorder as determined at Screening either by history or by the Mini International Neuropsychiatric Interview, Version 7.0.2 (MINI 7.0.2) Module A (Major Depressive Episode), Module C (Manic and Hypomanic Episodes), Module K (Psychotic Disorders), and Module O (Rule Out Medical, Organic, or Drug Causes for All Disorders).
4. History of or evidence for a diagnosis of borderline personality disorder (BPD) based on a score of ≥ 7 on the McLean Screening Instrument for BPD (MSI-BPD) at Visit 1 (Screening).
5. The patient is at increased risk of suicide on the basis of the Investigator's judgment, or the results of the C-SSRS conducted at Screening and Baseline (eg, any C-SSRS suicidal behavior or C-SSRS Type 3, 4, or 5 ideation during the preceding 6 months and any suicidal behavior within the past 12 months).
6. The patient has participated in any other study with TNX-102 SL.
7. The patient has a history of COVID-19 infection with a grading of ≥ 7 on the WHO COVID-19 8-Category Ordinal Scale of Disease Severity (Appendix 1).
8. Based on screening laboratory results, thyroid-stimulating hormone (TSH) > 1.5 times the upper limit of normal, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 times the upper limit of normal, or glycated hemoglobin (HbA1c) > 7.5%; or, in the Investigator's opinion, evidence of a clinically significant laboratory abnormality based on Screening laboratory tests or medical history.
9. Diagnosed with clinically significant and currently relevant cardiac disease (eg, significant arrhythmia; heart block; heart failure; symptomatic coronary artery disease or orthostatic hypotension), recent myocardial infarction [within the past 2 years]) or QTcF > 450 msec (male) or > 470 msec (female) on the screening electrocardiogram (ECG).
10. The patient currently has or has a history of a clinically significant systemic infection (eg, human immunodeficiency virus [HIV], hepatitis B or C).
11. The patient is currently receiving or is expected to need systemic corticosteroids (> 5 mg prednisone or equivalent per day) or has received acute treatment with systemic corticosteroids within 28 days of the Baseline Visit, or is likely to require such treatment during the study.
12. The patient has received tender point, trigger point, or other local injections with anesthetic agents (or corticosteroids, as per Exclusion Criterion #11) within 28 days of the Baseline Visit, or is unable to refrain from such injections during the study.
13. The patient is unable to successfully washout of the following medications during Screening, or washout is inadvisable: monoamine oxidase inhibitors (30-day washout required), levomilnacipran, anticonvulsants (aside from those used as migraine prophylaxis), amphetamine mixed salts, weight loss agents such as phentermine and diethylpropion, muscle relaxants (eg, methocarbamol, baclofen, carisoprodol, cyclobenzaprine), stimulants (eg, methylphenidate, lisdexamfetamine, dextroamphetamine), mirtazapine, trazodone, nefazodone, St. John's wort, any

medication known to be a strong CYP3A4 inhibitor (Appendix 5), or any of the medications listed in Inclusion Criterion #12.

14. Positive results for illegal or abused substances other than cannabis/THC at Screening or Baseline or history of substance use disorder during the preceding 1 year as defined by the screening MINI 7.0.2 Module J (Substance Use Disorder). Patients who utilize alcohol and/or cannabis/THC but do not meet criteria for greater than MILD Alcohol Use Disorder in Module I (Alcohol Use Disorder) and/or MILD Cannabis Use Disorder in Module J in the preceding 1 year are suitable for the study provided that, in the judgment of the Investigator, this usage will not interfere with the patient's ability to complete the study or provide reliable data.
15. Use of chewing or dipping tobacco or betel nut in the previous 6 months.
16. Planned use of teeth-whitening strips or prescription teeth-whitening products over the course of study participation.
17. Any existing oral, medical, or dental condition that could potentially interfere with the sublingual administration of study drug, the tolerability of study drug or the evaluation of administration site reactions.
18. Any history of severe or unexplained oral or oropharyngeal swelling or edema.
19. The patient has any clinically significant, uncontrolled, or unstable medical or surgical condition that could affect his or her ability to participate in the study or potentially compromise his or her well-being during the study. Patients with history of malignancy within 5 years of screening (other than treated carcinoma *in situ* of the cervix, basal cell carcinoma or Type 1 squamous cell carcinoma of the skin) must receive Medical Monitor approval prior to randomization.
20. The patient has an anticipated need for surgery that might confound results or interfere with his or her ability to comply with the protocol.
21. The patient is pregnant or nursing.
22. The patient has a hypersensitivity to cyclobenzaprine or the excipients in TNX-102 SL or placebo formulations or any contraindications to the use of cyclobenzaprine (such as history of urinary retention or increased intraocular pressure).
23. The patient has a seizure disorder or neuropathic pain that requires anticonvulsant therapy.
24. The patient has a history of sleep apnea that is severe, uncontrolled, or untreated. Patients with mild obstructive sleep apnea (eg, apnea/hypopnea index 5–15), and/or patients whose mild to moderate sleep apnea is well-controlled with continuous positive airway pressure or oral device, are allowed at the discretion of the Investigator.
25. The patient has a BMI > 38.0 kg/m^2 (due to the increased risk of sleep apnea).
26. The patient has a history of narcolepsy, cataplexy, restless leg syndrome, periodic involuntary limb movement disorder or other documented, clinically significant sleep disorder.

27. The patient has plans for international travel or has a work schedule (eg, requiring night shifts) that prevents them from being able to utilize the diary system during its available time window or to take study medication on a regular basis.
28. The patient is currently being treated with immunosuppressive medication, sodium oxybate, ketamine, esketamine, or calcitonin gene-related peptide (CGRP) receptor antagonists.
29. The patient has received an investigational CGRP receptor antagonist within 90 days of Screening, or any other investigational drug within 30 days of Screening.
30. The patient is currently receiving other therapies to treat acute COVID-19 symptoms or severity, such as convalescent plasma, remdesivir, or dexamethasone
31. The patient has another active systemic bacterial or fungal infection, or the patient is taking medications to treat another type of active infection

8.4. Randomization Criteria

Only those patients meeting all of the following randomization criteria at Visit 2 are eligible for randomization:

1. Continues to meet all inclusion and exclusion criteria, including urine and blood test results, and is successfully and consistently utilizing the diary system.
2. Patient's pain satisfies the following criteria, as assessed by diary pain scores (24-hour recall):
    a. A mean worst daily Long COVID pain intensity score ≥ 4 and ≤ 9 on the 11-point (0−10) NRS for the 7 days immediately preceding Visit 2, and
    b. No more than 2 individual days with a Long COVID pain score < 4 on the 7 days immediately preceding Visit 2, and
    c. No score of 10 on any of the 7 days immediately preceding Visit 2, and
    d. Long COVID pain scores recorded on at least 5 out of the 7 days immediately preceding Visit 2.

8.5. Patient Withdrawal Criteria

In accordance with the Declaration of Helsinki, patients have the right to withdraw from the study at any time for any reason. The Investigator and Tonix also have the right to remove patients from the study. Additional information regarding withdrawal or discontinuation of patients is described in detail in Section 11.6.2.

9. TREATMENT OF PATIENTS

9.1. Prior and Concomitant Medications

Patients who are taking certain medications are eligible for the study if they are willing and able, and it is medically reasonable, for them to be withdrawn from these medications prior to randomization and then refrain from usage during this study. The specific medications that must be withdrawn include duloxetine, milnacipran, pregabalin, gabapentin and other forms of anticonvulsants, tramadol, tapentadol, amitriptyline and other tricyclic antidepressants, trazodone, narcotics/opioids, naltrexone (including CONTRAVE®), all other forms of cyclobenzaprine (AMRIX®, or generic equivalents), orexin receptor antagonists, and benzodiazepines.

Therapies used to treat acute COVID-19 symptoms or severity, such as convalescent plasma, remdesivir, or dexamethasone will be prohibited.

Due to the exclusion of all opioids (including tramadol and tapentadol) during the treatment phase of the study, patients requiring opioids on a regular or frequent basis for any indication should not be considered. In addition, patients who are taking gabapentin, pregabalin, or any other anticonvulsant due to neuropathic pain should not be considered.

Other prescription or over-the-counter medication not specifically excluded by entry criteria may be continued during the study, provided that the patient has been on this medication at a stable dose for at least 4 weeks (except for allowed antidepressants, which require 90 days at stable dose) prior to randomization and is not expecting to change dosages during the period of the study.

In addition, certain other medications will also be prohibited and may require washout or exclusion of the patient if washout is not appropriate (eg, trazodone, mirtazapine, levomilnacipran, nefazodone, benzodiazepines, non-benzodiazepine sleep aids, stimulants, sodium oxybate, ketamine, esketamine, etc.).

Patients using teeth-whitening products such as whitening strips or prescription whitening products must agree to discontinue their use from the day of randomization until the end of their study participation.

After randomization, sedating antihistamines (eg, diphenhydramine, hydroxyzine) can be used as needed for insomnia; however, patients must be able to discontinue them during the Screening phase and must refrain from their use during the week of baseline data collection preceding Visit 2. The use of sedating anti-histamines after randomization should always be under the direction of the Investigator, and such use should be minimized to no more than a few nights in a row, followed by attempts to refrain from use.

The use of non-prescription nutraceuticals such as melatonin, ramelteon, and valerian root is not restricted.

New medications that are deemed required, in the opinion of the Principal Investigator or another physician, will be allowed, including medications needed to treat AEs. If there is a requirement for acute opioids, corticosteroids, or other treatments that could confound the evaluation of pain throughout the treatment period, the Investigator may consult with the Medical Monitor to

potentially delay the study visit until the medication is no longer needed. At a minimum, no opioid/narcotic should have been utilized within 2 days of a study visit, and ideally there will have been no usage during the 7 days prior to any visit, since important efficacy data will be collected on the diary during the week leading up to each visit.

Rescue medications used by patients throughout the study will be identified and documented during study visits.

9.2. Alcohol and Cannabis/THC Use

Patients utilizing cannabis/THC and alcohol are to be excluded if MINI 7.0.2 Module J criteria are met for greater than MILD Cannabis Use Disorder or greater than MILD Alcohol Use Disorder in Module I during the preceding 1 year (prior to the Screening Visit), OR if the Investigator is concerned that the patient's use of cannabis/THC or alcohol could interfere with patient's ability to provide reliable data or comply with the protocol. Cannabis/THC and alcohol use is otherwise allowed, with caution. The screening drug screen will also test for THC to provide the Investigator with information regarding exposure, and to ensure that all usage is disclosed and taken into consideration when conducting MINI Module J.

9.3. Enrollment of Patients

Before undergoing any study-related screening procedures, each potential patient must provide written informed consent. The Investigator will then determine the potential patient's suitability for the study by interviewing the patient and by performing per-protocol Screening assessments. Pre-randomization Approval by Tonix Pharmaceuticals will be required prior to Visit 2 in addition to satisfying all other eligibility and randomization criteria. If excluded medications are to be withdrawn for the explicit purpose of participation in this study, the patient must have already provided consent and signed an ICF before the withdrawal or down-titration of any medication is initiated.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug Packaging, Labeling, and Storage

Study drug supplies will be packaged identically so as to maintain the integrity of the study blind. The study drug bottles will be labeled minimally with the following information: study number TNX-CY-PA201, Sponsor name and address, bottle number, quantity, storage conditions, usage instructions, and caution statements for investigational new drug, ie, Caution: New Drug – Limited by United States Law to Investigational Use, and Keep Out of Reach of Children and Pets.

Each study drug bottle will contain 40 tablets. One bottle will be dispensed to each patient at Visit 2 (Baseline), and then 2 bottles will be dispensed at Visit 3 (Week 2), Visit 4 (Week 6), and Visit 5 (Week 10). This will provide the patient with enough tablets to cover the 2 or 4 weeks of dosing between visits, plus additional tablets to cover loss and/or visit window variability. The patient should be instructed to take all the tablets in one bottle before opening the second bottle. The patient should be instructed to keep this study drug in a safe location out of extreme environmental conditions and out of the reach of children and pets, and be instructed that this drug is not to be taken by any individual other than the study patient. Each patient will also be instructed that they are expected to return both bottles (even if empty) and all unused study drug at each clinic visit; unused drug will be counted to assess compliance with study drug treatment.

Storage of the study drug at the investigational site should be under locked and secure conditions with limited staff access. Study drug should be stored at 20−25°C/68−77°F in a temperature/humidity-monitored room; however, additional details on acceptable brief excursions and other pertinent information will be provided to the site.

10.2. Dosing Instructions

Patients will be instructed to take 1 tablet of randomly assigned study drug TNX-102 SL 2.8 mg or placebo tablet sublingually (under the tongue) each evening at bedtime starting at bedtime on Day 1 (Day of Visit 2) and continuing through Day 14. At the Week 2 Visit, patients will be instructed to increase the dose to 2 tablets at bedtime, administered simultaneously and under the tongue beginning on Day 15 and continuing through the end of the study.

The study drug should be taken at bedtime after teeth brushing and other oral care has been completed. The mouth/sublingual area should be moist at the time of dosing, so the patient should drink a few sips of water prior to dosing, especially if prone to dry mouth. Patients will be instructed to place the 1 or 2 SL tablets under their tongue (if 2, placed simultaneously under tongue) and keep them there until they have dissolved (approximately 90 seconds). They should not swallow, crush, or chew the tablets. Patients should not eat, drink, or chew gum for at least 15 minutes after dosing, and preferably not drink any hot, cold, or acidic beverage until morning. Patients also should not talk for at least 5 minutes after placing the study drug in the mouth (under the tongue). Patients will be reminded that only 2 tablets are allowed per day. Note: If the patient misses a dose, instruct the patient to continue dosing with 2 tablets the next evening; ie, they should not take more to make up for the missed dose.

If the patient reports intolerable side effects that are likely to result in premature discontinuation from the study, then the dose of study drug may be reduced to 1 tablet sublingually nightly, with

Medical Monitor approval. Any reduction in study drug dose must be documented in the case report form (CRF). The goal is for the patient to be on a stable and final dose of study drug starting from the Week 2 Visit, at the highest dose tolerated (preferably 2 tablets daily at bedtime). It is anticipated that only a few patients will require dosage reduction, as TNX-102 SL 5.6 mg has been well-tolerated in previous Phase 3 studies of TNX-102 SL. Moreover, the gradual titration from 1 tablet for the first 2 weeks to 2 tablets for the remainder of the study should help with acclimation to the higher dose.

10.3. Dispensing Instructions

Each patient who has met the randomization criteria (Section 8.4) will be assigned a double-blind treatment bottle at Visit 2 via the Interactive Response Technology (IRT), with a unique, but otherwise random bottle number that is generated when the study coordinator successfully completes randomization procedures. Patients will take one sublingual tablet each evening at bedtime for the first 2 weeks.

Beginning with the evening of the Week 2 Visit, patients will take 2 sublingual tablets each evening at bedtime, and will continue doing so throughout the course of the study. Only in the event of AEs that might possibly lead to discontinuation can the patient reduce the dose to 1 tablet per evening, with approval of the Principal Investigator and Medical Monitor.

Study treatments at maximum dosage for the double-blind treatment phase are either:

Treatment A: 2 × TNX-102 SL 2.8 mg tablets (“TNX-102 SL”) to be taken sublingually (simultaneously) once daily at bedtime.

Treatment B: 2 × placebo tablet (“placebo”) to be taken sublingually (simultaneously) once daily at bedtime.

In the event that a study drug bottle is lost, a new bottle will be provided by the IRT when appropriately requested by the site and/or the Sponsor or designee.

10.4. Release of Clinical Study Supplies to the Investigator

Tonix or Tonix’s designee’s Standard Operating Procedures for releasing clinical trial supplies to the site will be followed.

10.5. Study Drug Accountability and Reconciliation

All patients will be expected to bring their bottles of study drug with them to all study visits (including empty bottles). At each study visit, the site staff will inspect the drug bottles and perform a count of the tablets remaining in the bottles and document this in the patient’s record. An assessment of drug adherence should be done by the study staff to ensure that the patient understands all dosing instructions and is taking the drug as prescribed. Patients will be asked for an explanation if the count of returned study drug tablets indicates a discrepancy between the expected number of tablets dosed and the number returned in the bottles. If it is found that the patient is not taking the study drug as expected, the patient will be re-counseled with instructions, and this should be noted in the patients’ records. A deviation should be recorded on

any patient who is less than 70% compliant with dosing between visits, and a Medical Monitor should be contacted. In addition, if a patient fails to return >8 tablets within a 4-week (or >4 in a 2-week period), the PI is required to assess the patient for any potential drug abuse, misuse, or diversion. This assessment should be documented and reported within the Drug Accountability case report form.

Tonix or its designee will perform drug accountability, which entails reconciliation between the amount of drug shipped to the study site, study drug assigned and dispensed to the patient (including returned unused assigned study drug), and study supplies that were never dispensed and/or assigned to patients.

11. STUDY VISITS

The overall and detailed schedule for study procedures and visits is provided in Table 2.

11.1. Visit 1 (Screening Visit: Day -35 to Day -7)

11.1.1. Informed Consent

Before the potential patient has undergone any study-related screening procedures, including any down-titration or withdrawal of medications, the nature of the study and the potential risks associated with it will be explained to the patient, and the patient will be given an opportunity to ask questions to his or her satisfaction. After the questions are answered, but before proceeding further, the patient must read and sign a written ICF. This signed ICF will be retained in the Investigator's study file, and the date the patient signed the form will be entered into the CRF. The patient will be provided with a copy of his or her signed and dated ICF. The patient will be required to sign all updated ICFs.

11.1.2. Screening Overview

The first study visit, Screening Visit 1, will be when the study is thoroughly explained to the prospective patient, when written informed consent will be obtained and documented, and when certain protocol-specified study procedures and assessments will be completed. Screening Visit 1 will start a variable length Screening and Washout Period. The length of the Screening and Washout Period is to be no shorter than 7 days (since the "run-in" period during which baseline diary data are collected must be at least 7 days in duration), but may be as long as 35 days in order to accommodate medication washout or other study requirements. For extenuating circumstances, the total duration of the Screening period may be increased to up to a maximum of 49 days with Medical Monitor approval.

If the patient does not need to complete any medication washout, and assuming all screening procedures have been successfully completed and initial eligibility has been confirmed, then the patient may begin the 7-day run-in period as soon as the Screening Visit has been completed. Yet, due to potential delays in the issuance of a final laboratory report (eg, when a confirmatory analysis is required, typically on a urine drug screen analyte that is preliminarily positive), it is recommended that the Baseline Visit is scheduled at least 10 days from the Screening Visit. If the patient needs to complete medication washout prior to the start of the run-in period, the down-titration schedule for the patient and the date on which the patient should start the run-in period should be provided in writing to the patient. It is acceptable if another clinic visit is deemed necessary by the Investigator before initiating the run-in period (and should be recorded as an Unscheduled Visit). It is important to remember that any patient with a positive urine drug screen (UDS) (for a drug requiring washout) must return to the site for a repeat UDS prior to beginning their 7-day baseline data collection period. The repeat UDS for benzodiazepines must be centrally analyzed; all others may be performed on site. Patients who test positive for cannabis/THC at the Screening Visit but are deemed eligible to continue are not required to undergo repeat UDS testing.

11.1.3. Patient Numbering

All screened patients will be assigned a unique patient number.

11.1.4. Screening Assessments and Procedures

The following Screening assessments/procedures will be completed in the following general order:

- Obtain written informed consent to participate
- Check inclusion/exclusion criteria
- Collect demographics information
- Collect medical history
- Confirmation of prior SARS-CoV-2 infection
- Perform WHO COVID-19 severity classification
- Collect information on prior/concomitant medication
- Perform complete physical examination, including measurement of height and weight, and calculation of BMI
- Thorough examination of the oral cavity. This examination should include a careful visual examination of the sublingual area, tongue, buccal mucosa, lips, palate, and gums, aided with a tongue depressor, as well as palpation of the lips, hard palate, and floor of the mouth. Any abnormalities should be noted on the oral cavity examination source document.
- Administer Screening Visit Version of the mMBM
- Administer Mini International Psychiatric Interview 7.0.2 – Modules A (Major Depressive Episode), C (Manic and Hypomanic Disorders), I (Alcohol Use Disorder), J (Substance Use Disorder), K (Psychotic Disorders), and O (Rule Out Medical, Organic, or Drug Causes for All Disorders).
- Administer McLean Screening Instrument for Borderline Personality Disorder (MSI-BPD)
- Administer "Baseline/Screening" version of the Columbia-Suicide Severity Rating Scale (C-SSRS). Any patient with C-SSRS Type 3, 4, or 5 ideation during the preceding 6 months or any suicidal behavior during the preceding 1 year should be screen-failed
- Patient should complete the following patient-reported outcomes (PROs):
  a. NRS assessment of 7-day recall of average daily Long COVID pain. Patients should only continue screening if they score ≥ 4 and ≤ 9.
  b. PCFS scale
- Clinical laboratory tests, including serum chemistry, hematology, urinalysis,

- Viral laboratory tests, including serology for HIV, hepatitis B virus, and hepatitis C virus (HCV)
- Urine drug screening
- Serum pregnancy test for females of child-bearing potential (processed by central lab)
- Vital signs
- 12-lead electrocardiogram
- Only those patients meeting all of the inclusion and none of the exclusion criteria will be eligible to continue. Eligible patients will:
    a. Be asked to complete accurate pain reporting and placebo response reduction training.
    b. Be trained on the eDiary and instructed regarding the questions that will be asked of them. They will also receive information and materials necessary to initiate their daily diary record, along with information of what they are to do if they have difficulties recording their information. Patients will be asked to start the diary that evening. Due to limitations in the reporting window, patients who are planning on international travel during the study period or who work night shifts should not be considered for the study.
    c. Receive an appointment to return to the clinic for Visit 2.
    d. Receive a schedule for down-titration (if required) of any prohibited medications to be discontinued.

Pre-randomization Approval by Tonix Pharmaceutics will be required prior to Visit 2 in addition to satisfying all other eligibility and randomization criteria.

11.2. Visit 2 (Baseline: Day 1)

Visit 2 should be scheduled after the patient has completed their medication washout and completed at least 7 days of diary data entries. If the patient meets randomization criteria, the patient will be authorized to continue in the study. The patient will be randomized via the randomization system to receive double-blind study drug.

If the patient does not satisfy randomization criteria, the patient has failed to qualify for this study and should be considered a screen failure, with the reason documented. There is no requirement for a follow-up visit for screen failures.

11.2.1. Randomization Criteria

Only patients meeting all of the following randomization criteria will be eligible for randomization:

1. Continues to meet all inclusion and exclusion criteria, including urine and blood test results and is successfully and consistently utilizing the diary system.
2. Patient's pain satisfies the following criteria, as assessed by diary pain scores (24-hour recall):

a. A mean Long COVID pain intensity score ≥ 4 and ≤ 9 on the 11-point (0−10) NRS scale for the 7 days immediately preceding Visit 2; and

b. No more than 2 individual days with a Long COVID pain score < 4 on the 7 days immediately preceding Visit 2; and

c. No score of 10 on any of the 7 days immediately preceding Visit 2, and

d. Long COVID pain scores recorded on at least 5 out of the 7 days immediately preceding Visit 2.

11.2.2. Baseline Visit

For patients who have qualified for randomization, these assessments and procedures will be completed in the following general order:

- Collect any new medical history information
- Record any additional prior and concomitant medication use
- Targeted physical exam, focusing on previous and new findings and AEs
- Oral cavity examination. This examination should include a careful visual examination of the sublingual area, tongue, buccal mucosa, lips, palate, and gums. Any abnormalities should be noted on the oral exam source document. It is recommended that both non-significant as well as significant findings be noted so that there is a complete and accurate baseline assessment available for comparison to findings at later visits.
- Administer Baseline/Post-Randomization Version of the mMBM
- Administer the "Since Last Visit" version of the C-SSRS. Any patient exhibiting Type 3, 4, or 5 suicidal ideation or any suicidal behavior since the Screening Visit should be screen-failed and assessed for appropriate follow-up care.
- Patient should complete the following PROs:
  a. SDS
  b. PROMIS Short Form – Sleep Disturbance
  c. PROMIS Short Form v1.0 – Fatigue 8a
  d. PROMIS Short Form v1.0 – Cognitive Function - Abilities
  e. PCFS
  f. ISI
  g. ESS
- Administer urine pregnancy test for females of child-bearing potential (processed in-clinic)
- Vital signs

- Once it has been confirmed that the patient remains eligible, randomize patient via IRT Randomization System
- Assessment of eDiary compliance of 24-hour recall of worst Long COVID pain and sleep quality
- Assess occurrence of AEs
- Dispense bottle of double-blind study drug as assigned via the IRT
- Review patient instructions regarding study drug dosing and assess drug compliance (Section 10.2 and Section 12.1.8).
- Patients should complete the training on accurate pain reporting and placebo response reduction training as required.
- Optional blood draw for pharmacogenomics (after the separate ICF has been signed for the pharmacogenomic substudy) – It is preferred that the draw is done at the Baseline Visit (Visit 2); however, it can be drawn at a future visit.

11.2.3. Study Drug Dispensing

Qualified patients will be assigned a treatment bottle number via the randomization system (Section 10.3). The treatment bottle numbers are random and unique and will not necessarily be dispensed in any particular order. The treatment bottle number will be recorded in the patient's records.

11.2.4. Patient Instructions

After all assessments have been completed and before leaving the clinic at Visit 2, patients should:

- Be dispensed a single unopened bottle of double-blind study drug. The patient should be instructed to begin dosing with study drug at bedtime, starting the night of Visit 2.
- Receive instruction regarding proper sublingual dosing technique and the time of expected dosing.
- Receive reinforcement about the importance of completing all questions that will be asked on the daily diary and receive re-instruction, if necessary, on what they are to do if they have difficulties recording their information. NOTE: Patients should be instructed that they should complete their diary within the required time window.
- Receive an appointment for Visit 3.
- The patient should be instructed to call the site if they develop a lesion under the tongue or any other localized AE in the oral cavity thought potentially related to study drug exposure, specifically to determine if an Unscheduled Visit for an oral cavity examination is necessary prior to the next scheduled visit. Reports of oral numbness, tingling, or noticeable taste (eg, bitter, metallic, unpleasant) after dosing do not require unscheduled examinations.

11.3. Visit 3 (Week 2)

Visit 3 should occur after 2 weeks of treatment, on Day 15 -4 / +7 days. For those patients unable to return to the site (ie, extenuating circumstances due to COVID-19 pandemic), a telephone visit is an option.

The following assessments and procedures are scheduled for this visit in the following general order:

- Record concomitant medication use
- Examination of the oral cavity. Ensure that this exam includes the sublingual area and that any abnormalities are carefully described on the oral exam source document. (Telephone visit exception – visual exam of the oral cavity is not required – but in addition to standard inquiry about AEs, site staff will inquire specifically if there have been any changes or problems in the oral cavity. Patients reporting any concerning lesion description or painful processes in the oral cavity possibly related to study drug exposure should be strongly urged to come into the clinic for an Unscheduled Visit for oral cavity exam. In circumstances in which, due to the COVID-19 pandemic, it is not possible for the patient to return to the clinic for the Unscheduled Visit exam, a clinician certified by the Sponsor to conduct oral cavity examination should contact the patient by phone and obtain greater history and description of the oral cavity AE by patient, potentially augmented with images of oral cavity taken by the patient and sent to the site for the examining clinician to *textually* document in the oral exam source document. In such cases in which the patient is unwilling or unable to come in, Principal Investigator (PI) and Medical Monitor should also confer on whether study drug should be discontinued.)
- Administer Baseline/Post-Randomization Version of the mMBM
- Administer the “Since Last Visit” version of the C-SSRS. (Telephone visit exception: C-SSRS is administered over the phone)
- Patient should complete the following PROs (Telephone visit exception: all PROs should be mailed ahead of the visit and returned to the clinic after completion via courier):
  a. SDS
  b. PROMIS Short Form – Sleep Disturbance
  c. PROMIS Short Form v1.0 – Fatigue 8a
  d. PROMIS Short Form v1.0 – Cognitive Function - Abilities
  e. PGI-C
  f. ESS
- Administer urine pregnancy test for females of child-bearing potential (processed in-clinic). (Telephone visit exception: urine pregnancy test will be performed at home by patient for women of child-bearing potential).

- Record vital signs. (Telephone visit exception: vital signs are not required).
- Assessment of eDiary compliance of 24-hour recall of worst Long COVID pain and sleep quality. Discuss any compliance concerns with the patient and provide re-training as needed.
- Patients should complete the training on accurate pain reporting and placebo response reduction training as required.
- Assess study drug compliance and collect previously dispensed study drug and bottle. (Telephone visit exception: patient will be instructed to count the number of tablets remaining in their current bottle[s], document this on a patient provided form, and return this form with the study drug [including bottle(s)] to the site for assessment of compliance in a pre-paid pre-addressed courier envelope supplied in a "tele-visit" package to patient).
- Assess occurrence of AEs
- Discuss the scheduled increase in dose of study drug from 1 sublingual tablet (Days 1−14) to 2 tablets administered sublingually and simultaneously at bedtime throughout the remainder of the study (Days 15−99). Remind patient to contact the site for any issues regarding tolerability and to only make changes in dose under the direction of the Investigator.
- Dispense new bottles (unopened) of double-blind study drug as assigned by IRT. Patients should begin dosing from new study drug bottles on the evening of the visit. (Telephone visit exception: study drug will be mailed to the patient via courier. Patients should begin dosing from new study drug bottles on the evening of the visit).
- Confirm that the increase in drug dosing to 2 tablets sublingually at bedtime is understood by patient.
- Optional blood draw for pharmacogenomics (after the separate ICF has been signed for pharmacogenomic substudy) - if not drawn already at a prior visit

After all of the assessments at each visit have been completed, the patient should be given an appointment to return to the clinic for the next scheduled visit, and be re-instructed, as necessary, in the completion of the diary, dosing instructions, and reminded to bring all study drug (and bottles) back to the clinic at their next visit.

11.4. Visit 4 (Week 6)

Visit 4 should occur after 6 weeks of treatment, on Day 43 ± 7 days. For those patients unable to return to the site (ie, extenuating circumstances due to COVID-19 pandemic), a telephone visit is an option.

The following assessments and procedures are scheduled for this visit in the following general order:

- Record concomitant medication use

- Oral cavity examination. Ensure that this exam includes the sublingual area and that any abnormalities are carefully described on the oral exam source document. (Telephone visit exception: visual exam of the oral cavity is not required – but in addition to standard inquiry about AEs, site staff will inquire specifically if there have been any changes or problems in the oral cavity. Patients reporting any concerning lesion description or painful processes in the oral cavity possibly related to study drug exposure should be strongly urged to come into the clinic for an Unscheduled Visit for oral cavity exam. In circumstances in which, due to the COVID-19 pandemic, it is not possible for the patient to return to the clinic for the Unscheduled Visit exam, a clinician certified by the Sponsor to conduct oral cavity examination should contact the patient by phone and obtain greater history and description of the oral cavity AE by patient, potentially augmented with images of oral cavity taken by the patient and sent to the site for the examining clinician to *textually* document in the oral exam source document. In such cases in which the patient is unwilling or unable to come in, PI and Medical Monitor should also confer on whether study drug should be discontinued.)
- Administer Baseline/Post-Randomization Version of the mMBM
- Administer the "Since Last Visit" version of the C-SSRS. (Telephone visit exception: C-SSRS is administered over the phone)
- Patient should complete the following PROs (Telephone visit exception: all PROs should be mailed ahead of the visit and returned to the clinic after completion via courier):
  a. SDS
  b. PROMIS Short Form – Sleep Disturbance
  c. PROMIS Short Form v1.0 – Fatigue 8a
  d. PROMIS Short Form v1.0 – Cognitive Function - Abilities
  e. PGI-C
  f. ESS
- Clinical laboratory tests, including serum chemistry, hematology, urinalysis
- Administer urine pregnancy test for females of child-bearing potential (processed in-clinic). (Telephone visit exception: urine pregnancy test will be performed at home by patient for women of child-bearing potential).
- Record vital signs. (Telephone visit exception – vital signs are not required)
- Assessment of eDiary compliance of 24-hour recall of worst Long COVID pain and sleep quality Discuss any compliance concerns with the patient and provide retraining as needed.
- Patients should complete the training on accurate pain reporting and placebo response reduction training as required.

- Assess study drug compliance and collect previously dispensed study drug and bottle. (Telephone visit exception: patient will be instructed to count the number of tablets remaining in their current bottle[s], document this on a patient provided form, and return this form with the study drug [including bottle(s)] to the site for assessment of compliance in a pre-paid pre-addressed courier envelope supplied in a "tele-visit" package to patient).
- Assess occurrence of AEs
- Dispense new bottles (unopened) of double-blind study drug as assigned by IRT. Patients should begin dosing from new study drug bottles on the evening of the visit. (Telephone visit exception: study drug will be mailed to the patient via courier. Patients should begin dosing from new study drug bottles on the evening of the visit).
- Optional blood draw for pharmacogenomics (after the separate ICF has been signed for the pharmacogenomic substudy) - if not drawn already at a prior visit.

After all of the assessments at each visit have been completed, the patient should be given an appointment to return to the clinic for the next scheduled visit, and be re-instructed, as necessary, in the completion of the diary, dosing instructions, and reminded to bring all study drug (and bottles) back to the clinic at their next visit.

11.5. Visit 5 (Week 10)

Visit 4 should occur after 6 weeks of treatment, on Day 71 ± 7 days. For those patients unable to return to the site (ie, extenuating circumstances due to COVID-19 pandemic), a telephone visit is an option.

The following assessments and procedures are scheduled for this visit in the following general order:

- Record concomitant medication use
- Oral cavity examination. Ensure that this exam includes the sublingual area and that any abnormalities are carefully described on the oral exam source document. (Telephone visit exception: visual exam of the oral cavity is not required – but in addition to standard inquiry about AEs, site staff will inquire specifically if there have been any changes or problems in the oral cavity. Patients reporting any concerning lesion description or painful processes in the oral cavity possibly related to study drug exposure should be strongly urged to come into the clinic for an Unscheduled Visit for oral cavity exam. In circumstances in which, due to the COVID-19 pandemic, it is not possible for the patient to return to the clinic for the Unscheduled Visit exam, a clinician certified by the Sponsor to conduct oral cavity examination should contact the patient by phone and obtain greater history and description of the oral cavity AE by patient, potentially augmented with images of oral cavity taken by the patient and sent to the site for the examining clinician to *textually* document in the oral exam source document. In such cases in which the patient is unwilling or unable to come in, PI and Medical Monitor should also confer on whether study drug should be discontinued.)

- Administer Baseline/Post-Randomization Version of the mMBM
- Administer the "Since Last Visit" version of the C-SSRS. (Telephone visit exception: C-SSRS is administered over the phone).
- Patient should complete the following PROs (Telephone visit exception: all PROs should be mailed ahead of the visit and returned to the clinic after completion via courier):
    a. SDS
    b. PROMIS Short Form – Sleep Disturbance
    c. PROMIS Short Form v1.0 – Fatigue 8a
    d. PROMIS Short Form v1.0 – Cognitive Function - Abilities
    e. PGI-C
    f. ESS
- Administer urine pregnancy test for females of child-bearing potential (processed in-clinic). (Telephone visit exception: urine pregnancy test will be performed at home by patient for women of child-bearing potential).
- Record vital signs. (Telephone visit exception: vital signs are not required)
- Assessment of eDiary compliance of 24-hour recall of worst Long COVID pain and sleep quality. Discuss any compliance concerns with the patient and provide re-training as needed.
- Patients should complete the training on accurate pain reporting and placebo response reduction training as required.
- Assess study drug compliance and collect previously dispensed study drug and bottle. (Telephone visit exception: patient will be instructed to count the number of tablets remaining in their current bottles, document this on a patient provided form, and return this form with the study drug [including bottles] to the site for assessment of compliance in a pre-paid pre-addressed courier envelope supplied in a "tele-visit" package to patient).
- Assess occurrence of AEs
- Dispense new bottles (unopened) of double-blind study drug as assigned by IRT. Patients should begin dosing from new study drug bottles on the evening of the visit. (Telephone visit exception: study drug will be mailed to the patient via courier. Patients should begin dosing from new study drug bottles on the evening of the visit).
- Review patient instructions regarding diary completion.
- Optional blood draw for pharmacogenomics (after the separate ICF has been signed for the pharmacogenomic substudy) - if not drawn already at a prior visit.

After all of the assessments at each visit have been completed, the patient should be given an appointment to return to the clinic for the next scheduled visit, and be re-instructed, as necessary,

in the completion of the diary, dosing instructions, and reminded to bring all study drug (and bottles) back to the clinic at their next visit.

11.6. Visit 6 (Week 14 or Early Termination)

11.6.1. Visit 6 (Week 14)

Visit 6 should occur after 14 weeks of double-blind study drug treatment, scheduled at Day 99 -4 / +7 days. At this visit, the patient will return all study drug and be instructed that there is no longer any need to complete the diary. If circumstances involving the COVID-19 have resulted in the patient being reluctant to attend this visit at the clinic, it should be strongly emphasized that a complete safety assessment at end of study necessitates the in-person visit. If the patient absolutely refuses or it is impossible to attend the clinic because of a COVID-19 pandemic-related "stay at home" order or similar, the PI should discuss the case with the Medical Monitor. Approval for a Week 14 telephone visit may be granted by the Medical Monitors on a case by case basis. In cases in which it is feasible for a site's own research staff, with or without a research clinician, to make a home visit for Week 14/Visit 6 (or ET), a home visit should be conducted rather than a telephone visit in order to collect greater safety data than the telephone visits allow. Home visits may be conducted by any qualified staff member and will allow, in addition to all procedures conducted in a telephone visit, collection of vital signs and weight, and venipuncture for Week 14/ET laboratory tests and, for women of child-bearing potential, collection of urine specimen for pregnancy test upon return to site. Home visits that include a clinician certified by Sponsor to conduct the oral cavity exam will additionally be able to include an oral cavity examination and a brief physical examination, allowing completion of all Week 14/ET safety assessments.

The following assessments and procedures are scheduled for this visit in the following general order:

- Record concomitant medication use
- Perform brief physical examination, including measurement of weight and calculation of BMI (Telephone visit exception: brief physical exam is not required).
- Oral cavity examination. Ensure that this exam includes the sublingual area and that any abnormalities are carefully described on the oral exam source document. (Telephone visit exception: visual exam of the oral cavity is not required – but in addition to standard inquiry about AEs, site staff will inquire specifically if there have been any changes or problems in the oral cavity. Patients reporting any concerning lesion description or painful processes in the oral cavity possibly related to study drug exposure should be strongly urged to come into the clinic for an Unscheduled Visit for oral cavity exam. In circumstances in which, due to the COVID-19 pandemic, it is not possible for the patient to return to the clinic for the Unscheduled Visit exam, a clinician certified by the Sponsor to conduct oral cavity examination should contact the patient by phone and obtain greater history and description of the oral cavity AE by patient, potentially augmented with images of oral cavity taken by the patient and sent to the site for the examining clinician to *textually* document in the oral exam source document.)

- Administer Baseline/Post-Randomization Version of mMBM
- Administer the "Since Last Visit" version of the C-SSRS. (Telephone visit exception: C-SSRS is administered over the phone).
- Patient should complete the following PROs (Telephone visit exception: all PROs should be mailed ahead of the visit and returned to the clinic after completion via courier):
  a. SDS
  b. PROMIS Short Form – Sleep Disturbance
  c. PROMIS Short Form v1.0 – Fatigue 8a
  d. PROMIS Short Form v1.0 – Cognitive Function - Abilities
  e. PGI-C
  f. PCFS
  g. ISI
  h. ESS
- Clinical laboratory tests, including serum chemistry, hematology, urinalysis. (Telephone visit exception: laboratory tests are not required).
- Administer urine pregnancy test for females of child-bearing potential (processed in-clinic). (Telephone visit exception: urine pregnancy test will be performed at home by patient for women of child-bearing potential).
- Record vital signs (Telephone visit exception: vital signs are not required).
- Assessment of eDiary compliance of 24-hour recall of worst Long COVID pain and sleep quality. Discuss any compliance concerns with the patient and provide re-training as needed.
- Assess study drug compliance and collect previously dispensed study drug and bottle. (Telephone visit exception: patient will be instructed to count the number of tablets remaining in their current bottles, document this on a patient provided form, and return this form with the study drug [including bottles] to the site for assessment of compliance in a pre-paid pre-addressed courier envelope supplied in a "tele-visit" package to patient).
- Assess occurrence of AEs.
- Optional blood draw for pharmacogenomics (after the separate ICF has been signed for the pharmacogenomic substudy) - if not already drawn at a prior visit.

11.6.2. Early Termination (Post-Randomization)

In accordance with the Declaration of Helsinki, patients have the right to withdraw from the study at any time for any reason, and they will be advised of this right. The Investigator and

Tonix also have the right to remove patients from the study. Specific reasons for removal of a patient from the study could include, but are not limited to:

- An AE
- An illness that, in the judgment of the Investigator or Tonix, might invalidate the study data or place the patient at risk
- The request of the patient, Investigator, or Tonix, whether for administrative or other reasons
- Pregnancy

Patients who wish to terminate their participation in the study should be instructed to come to the clinic for an ET Visit. The purpose of the ET Visit is to obtain critical information about the patient's participation and should be scheduled preferably before there has been a substantial lapse in study drug usage. However, even if there has been a drug lapse, the patient should be encouraged to return to the clinic for this visit and should be instructed to return all study drug and bottles. NOTE: These visit procedures are not intended for patients who fail to qualify for randomization or for patients who withdraw from the study prior to receipt of a dose of double-blind study drug.

The following assessments and procedures are completed at this visit as ordered below:

- Document reason for early termination
- Perform brief physical examination, including weight and BMI (Telephone visit exception: brief physical exam is not required)
- Record concomitant medication use
- Oral cavity examination. Ensure that this exam includes the sublingual area and that any abnormalities are carefully described on the oral exam source document. (Telephone visit exception: visual exam of the oral cavity is not required – but in addition to standard inquiry about AEs, site staff will inquire specifically if there have been any changes or problems in the oral cavity. Patients reporting any concerning lesion description or painful processes in the oral cavity possibly related to study drug exposure should be strongly urged to come into the clinic for an unscheduled visit for oral cavity exam). In circumstances in which, due to the COVID-19 pandemic, it is not possible for the patient to return to the clinic for the Unscheduled Visit exam, a clinician certified by the Sponsor to conduct oral cavity examination should contact the patient by phone and obtain greater history and description of the oral cavity AE by patient, potentially augmented with images of oral cavity taken by the patient and sent to the site for the examining clinician to *textually* document in the oral exam source document.)
- Administer Baseline/Post-Randomization Version of the mMBM
- Administer the "Since Last Visit" version of the C-SSRS (Telephone visit exception: C-SSRS is administered over the phone).

- Have the patient complete all PROs: (Telephone visit exception: all PROs should be mailed ahead of the visit and returned to the clinic after completion via courier):
  a. SDS
  b. PROMIS Short Form – Sleep Disturbance
  c. PROMIS Short Form v1.0 – Fatigue 8a
  d. PROMIS Short Form v1.0 – Cognitive Function - Abilities
  e. PGI-C
  f. PCFS
  g. ISI
  h. ESS
- Clinical laboratory tests, including serum chemistry, hematology, urinalysis. (Telephone visit exception: laboratory tests are not required).
- Administer urine pregnancy test for females of child-bearing potential (processed in-clinic). (Telephone visit exception: urine pregnancy test will be performed at home by patient for women of child-bearing potential).
- Record vital signs (Telephone visit exception: vital signs are not required).
- Assessment of eDiary compliance of 24-hour recall of worst Long COVID pain and sleep quality. Discuss any compliance concerns with the patient and provide re-training as needed. Assess study drug compliance and collect previously dispensed study drug and bottle. (Telephone visit exception: patient will be instructed to count the number of tablets remaining in their current bottles, document this on a patient provided form, and return this form with the study drug [including bottles] to the site for assessment of compliance in a pre-paid pre-addressed courier envelope supplied in a "tele-visit" package to patient).
- Assess occurrence of AEs.
- Optional blood draw for pharmacogenomics (after the separate ICF has been signed for the pharmacogenomic substudy) - if not already drawn at a prior visit.

Once these assessments have been completed, the patient may be discharged from the study, provided that there is no need for additional follow-up to continue to monitor an AE or other condition. All participants will receive two safety follow-up phone calls approximately 2 and 4 weeks later (Visits 7 and 8).

11.7. Visit 7 (Week 16/Post-study Safety Follow-up)

Visit 7 should occur approximately 2 weeks ± 7 days after Visit 6/ET. This visit will be performed by telephone, to collect any additional data on concomitant medication and AEs and the general condition of the patient.

11.8. Visit 8 (Week 18/1-Month Post-study Safety Follow-up)

Visit 8 should occur approximately 4 weeks ± 7 days after Visit 6/ET. This visit will be performed by telephone, to collect any additional data on concomitant medication and AEs and the general condition of the patient.

11.9. Unscheduled Visit

Patients may need to be seen at other times than the scheduled study visits for additional safety assessments or to follow-up, as medically necessary, on clinical laboratory, physician examination, or other findings. If an additional study visit is warranted, or occurs, the date and nature of the visit will be documented in the CRF and in the source documents.

Patients should contact the investigative site as soon as possible if they experience a lesion under the tongue or any other oral cavity AE potentially related to study drug exposure (other than transient numbness, tingling, or bitter/metallic/unpleasant taste after dosing), specifically to determine if they should return to the clinic for an unscheduled oral cavity examination.

Note: If an AE is ongoing at the time of the Week 14/ET visit or there is suspicion that an AE has occurred due to the drug even after discontinuation, the patient may be brought in for an unscheduled in-person visit for additional follow-up.

12. STUDY ASSESSMENTS

The primary efficacy endpoint and many of the secondary and exploratory efficacy endpoints in this study are derived from patient-completed assessments. Therefore, it is critical that these assessments are conducted in the specified order, according to specific instructions, and in a setting where the patient has minimal distractions and sufficient time to complete them. After completion of these assessments, the study coordinator, unless specifically prohibited by instrument instructions, should review the responses for completeness with the patient.

12.1. Efficacy Assessments

12.1.1. Modified Michigan Body Map

The MBM is based on the 2011 FM Survey Criteria, a tool that is commonly used to assess for the presence of multi-site pain in FM, a disorder characterized by widespread body pain, along with comorbid symptomatology similar to that experienced by patients with Long COVID. The 2011 FM Survey Criteria include the assessment of pain in 19 specific body areas using the Widespread Pain Index (WPI). The areas from the WPI are then combined with the Symptom Severity scale to assess the presence and severity of FM (Wolfe et al. 2010; Wolfe et al. 2011). The MBM is a graphic mannequin with the 19 areas from the WPI superimposed upon it in anatomically relevant locations. The MBM also contains 16 additional areas for more general use. The MBM, and its online version, have been validated in patients with chronic pain (Brummett et al. 2016; Hassett et al. 2019).

Tonix Pharmaceuticals has modified the MBM (mMBM) in consultation with its authors. [redacted]

[redacted]

12.1.2. Sheehan Disability Scale (SDS)

SDS is a brief self-reporting tool that rates the extent to which work/school, social life, and home life or family responsibilities are impaired by the symptoms on a 10-point visual analog scale (Williams et al. 2000; Appendix 6). The 3 items can also be summed into a single dimensional measure of global functional impairment that ranges from 0 (unimpaired) to 30 (highly impaired). SDS will be administered as shown in Table 2.

12.1.3. PROMIS Scales

PROMIS is the Patient-Reported Outcome Measurement Information System (www.nihpromis.org), an NIH-funded initiative to develop instruments to be used across chronic conditions.

Three PROMIS Scales will be assessed in this study, including the Sleep Disturbance scale (version 8a) (Appendix 7), the Fatigue scale (version 8a) (Appendix 8,) and the Cognitive Function – Abilities scale (version 8a) (Appendix 9). Each of these scales will be assessed as shown in Table 2.

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

The PGI-C is a validated instrument to gauge the patient's assessment of change in condition (Guy. 1976; Dworkin et al. 2008;

Appendix 10). This form will be completed by the patient at time points shown in Table 2.

12.1.5. Post-COVID-19 Functional Status (PCFS) scale

PCFS scale is an ordinal scale for assessment of patient-relevant functional limitations over time after COVID-19 infection (Klok et al 2020; Machado et al 2021; available at https://osf.io/qgpdv/; Appendix 4). The PCFS scale will be administered as shown in Table 2.

12.1.6. Insomnia Severity Index (ISI) – Patient version

The ISI is a 7-item self-reported questionnaire assessing the nature, severity, and impact of insomnia (Spielman et al. 1987; Morin et al, 2011; Appendix 11).

The usual recall period is the "last month" and the dimensions evaluated are severity of sleep onset, sleep maintenance and early morning awakening problems, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, noticeability of sleep problems by others, and distress caused by the sleep difficulties. The ISI questionnaire will be administered as shown in Table 2.

The scores range from 0 (no problem) to 4 (very severe problem) yielding a total score ranging from 0 to 28. The total score is interpreted as:

0–7 = absence of insomnia
8–14 = sub-threshold insomnia
15–21 = moderate insomnia
22–28 = severe insomnia

12.1.7. Epworth Sleepiness Scale (ESS)

The ESS is a self-administered questionnaire with 8 questions (Johns 1991; Appendix 12). The patient rates from 0 to 3 their usual chances of dosing off or falling asleep while engaged in 8 different activities. The total score can range from 0 to 24, with higher rating indicating higher average sleep propensity in daily life. The ESS questionnaire will be administered as shown in Table 2.

12.1.8. eDiary

The daily eDiary is an important aspect of this study, and all patients must receive training explaining what is being asked of them, when to complete the diary, and how to use the diary system effectively. Patients will be trained on use of the diary system at Visit 1. Additionally, patients should complete the training on accurate pain reporting and placebo response reduction training as required.

During the 7-day run-in Phase (7 days immediately preceding Visit 2 [Baseline/Randomization Visit; Day 1]) patients will be asked to record their worst daily Long COVID pain intensity on the 11-point (0−10) NRS scale using 24-hour recall and to assess sleep quality from the previous evening, also using an 11-point NRS scale. The average of the 7 days immediately preceding Visit 2 (Baseline Randomization Visit; Day 1) will serve as the Baseline pre-treatment scores.

During the treatment phase, each evening, the system will prompt the patient to reflect on the past 24 hours and record their worst pain intensity, assess their sleep quality from the previous evening, and log study drug dosing from the previous night (post--randomization).

Patients will receive instructions and a password that uniquely identifies them when they log into the diary system, along with instructions about what to do if they have difficulty completing the diary.

The diary should be started the evening of Visit 1 and completed daily until Visit 6 (Week 14). Patients should be instructed to complete the diary in the evening before dosing. Once the patient has properly identified themselves, the diary will prompt answers to the following:

- Rate your worst Long COVID pain intensity during the last 24 hours on a scale from 0-10, where 0 is “no pain” and 10 is “pain as bad as you can imagine”. Rate your sleep quality last night on a scale from 0−10 where 0 is the “best possible sleep” and 10 is the “worst possible sleep”.

After randomization to study drug at Visit 2, the following questions will be added to the daily diary (starting in the evening of the day after randomization, Day 2):

- Did you take your study drug last night? (Yes/No)
- If yes, how many tablets of study drug did you take last night? (1 tablet/2 tablets)

Appendix 13 details additional information about the eDiary.

The study staff will be expected to monitor patient compliance throughout the study and will be instructed to call the patient should any problems or significant non-compliance be observed. During the Screening period, there are diary compliance requirements that must be met in order for the patient to qualify for randomization. Patients will receive a reminder to complete their diary if they miss diary entries. Patients who miss 2 diary entries will be flagged by the IRT system, and site staff will be alerted to contact patients for re-training and to instruct the patient on the importance of routine completion of their diary.

12.2. Safety Assessments

Safety will be assessed by evaluation of AEs, vital signs, responses on the C-SSRS, and by clinical laboratory and physical examination findings, including visual inspection of the oral cavity.

12.2.1. Adverse Events

Patients will be monitored for AEs throughout the study. Any clinically significant abnormal findings at Screening should be recorded in medical history. AEs will be recorded after the informed consent is signed. AEs that are spontaneously reported or elicited or observed are to be recorded on the CRF with the date, time of onset, date and time of resolution, severity, seriousness, causality (relationship to study drug), actions required, and outcome. Additional questions will be triggered for AEs involving the oral cavity (Section 12.2.5).

To elicit AEs, non-leading, simple questions with minimal connotations should be used as the initial questions at all evaluation points during the study. Examples of these questions can be:

- How have you felt since your last visit?
- Have you had any health problems since your last visit?

If an AE occurs, the Investigator will institute support and/or treatment as deemed appropriate. If an AE is unresolved on the last day of the study, an effort should be made to follow up until the AE is resolved or stabilized, the patient is lost to follow-up, or there is some other resolution of the event.

There are many symptoms associated with Long COVID that can vary in intensity and frequency over time. Only symptoms that worsen or become more frequent and, in the opinion of the patient, are outside of their normal experience should be reported as AEs.

Additional information regarding definition and reporting requirements for AEs, serious adverse events (SAEs), and pregnancies is provided in Section 14.

12.2.2. Oral Adverse Events

Patients should contact the investigative site as soon as possible if they experience a lesion under the tongue or any other AE thought to be due to study drug exposure (other than transient numbness, tingling or bitter/metallic/unpleasant taste after dosing), specifically to determine whether an Unscheduled Visit is necessary prior to the next scheduled visit. If the patient does not call the site to discuss the oral cavity AE, the oral cavity exam should be performed at the next regularly scheduled visit and any findings noted. If a telephone visit, the patient should be queried if there have been any changes or problems in the oral cavity. Patients reporting any concerning lesion description or painful processes in the oral cavity possibly related to study drug exposure should be strongly urged to come into the clinic for an Unscheduled Visit for an oral cavity exam. This exam must be performed by a qualified licensed medical professional who has been specifically trained and certified by the Sponsor to conduct this exam. In circumstances in which, due to the COVID-19 pandemic it is not possible for the patient to return to the clinic for the Unscheduled Visit exam, a clinician certified by the Sponsor to conduct oral cavity examination should contact the patient by phone and obtain greater history and description of the oral cavity AE by patient, potentially augmented with images of oral cavity taken by the patient and sent to the site for the examining clinician to textually document in the oral exam source document.

12.2.3. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a questionnaire developed by researchers at Columbia University to assess and track suicide risk and behavior. This scale is intended to be used by individuals who have received training in its administration. The questions contained in the C-SSRS are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Two versions of this questionnaire will be utilized in this study. At Visit 1, the "Baseline/Screening" questionnaire will be administered, and the recall periods will be "lifetime" and "within the past 6 months" for suicidal ideation and "within the past 1 year" for suicidal

behavior. Patients whose responses are indicative of suicidal ideation with intent and/or plan (eg, Type 3, 4, or 5 suicidal ideation) within the past 6 months or a history of suicidal behavior within the past year will be excluded from participation, with recommended referral for appropriate intervention.

At all subsequent visits (Visits 2, 3, 4, 5, and 6), the "Since Last Visit" version of the questionnaire will be administered, and the recall period on this will be "since the last visit".

12.2.4. Physical Examination and Vital Signs

A complete physical examination will be performed at Visit 1. The complete physical examination may exclude rectal, genitourinary, and breast examinations.

Vital signs (sitting blood pressure and heart rate, temperature, and weight) will be assessed at Visits 1, 2, 3, 4, 5, and 6/ET (unless a telephone visit, in which case vital signs will not be assessed at Visits 3, 4, 5, and 6/ET). Height will be measured without shoes at Visit 1 only. The BMI will be a derived variable, based on height and weight entries (but a Week 14/ET weight will not be assessed, if approved by the Medical Monitor for a telephone visit).

12.2.5. Visual Examination of the Oral Cavity

A thorough examination (visual plus palpation) of the oral cavity will be completed at Visit 1, with visual examinations performed at each subsequent study visit (Visits 2, 3, 4, 5 and 6/ET). Visual exam of the oral cavity will not be performed if it is a telephone visit. This examination should include a careful visual examination of the sublingual area, tongue, buccal mucosa, lips, palate, and gums, aided with a tongue depressor, as well as palpation of the lips, hard palate, and floor of the mouth.

Each examination must be performed by a qualified medical professional who has been specifically trained and certified by the Sponsor for this examination. An oral cavity examination may also be required at an Unscheduled Visit if a patient reports an oral AE that requires follow-up prior to the next scheduled visit.

12.2.6. Clinical Laboratory Assessments

The clinical laboratory evaluations to be performed in this trial are listed in Table 3. Those marked as screening tests will be performed at Screening only. All other tests will be performed at the Screening Visit, Visit 4/Week 6, and at Visit 6/ET (Week 14), aside from urine pregnancy tests and ad hoc urine drug screens. Testing for HIV, HCV, and hepatitis B surface antigen (HBsAg) will be performed at Screening and may be performed at other visits at Investigator's or Sponsor's discretion.

With the exception of the urine pregnancy test or an ad hoc urine drug screen, all clinical laboratory evaluations will be analyzed via a central clinical laboratory, and information regarding appropriate sample volume, collection tubes, sample labeling and handling, and shipment will be provided in the clinical laboratory manual.

As per Exclusion Criterion #14 any patient with evidence during the preceding year of drug or alcohol use disorder by MINI or history is ineligible.

A centrally analyzed UDS will be performed at Visit 1. If the patient has a positive drug screen at Visit 1 due to a drug of abuse (eg, cocaine, methamphetamine, ecstasy) or due to a non-disclosed opioid, amphetamine, or benzodiazepine, then he/she should be screen-failed. As discussed in Section 9.2, patients utilizing cannabis/THC are to be excluded if MINI criteria are met for greater than MILD Cannabis Use Disorder during the preceding 12 months, OR if the Investigator is concerned that the patient's use of cannabis/THC could interfere with patient's ability to provide reliable data or comply with the protocol. Otherwise, patients utilizing cannabis or THC products are allowed, with caution.

The screening drug screen will test for THC to provide the Investigator with information regarding exposure, and to ensure that all usage is disclosed and taken into consideration when conducting MINI Module J. Repeat testing of THC is not necessary for patients testing positive for cannabis/THC at screening.

Any patient deemed appropriate for washout of a prescription opioid, benzodiazepine, or amphetamine will require a repeat UDS before the beginning of their 7 days of baseline data collection leading up to Visit 2, the results of which must be negative and available for review before randomization may occur. Therefore, these patients will need to return for an Unscheduled Visit after the first 2 weeks of Washout have been completed. All benzodiazepine drug screening must be sent to the central laboratory for analysis; hence, results may be delayed. All other repeat urine drug screening may be conducted on site. Patients do not have to wait for confirmation of negative centralized benzodiazepine results before starting their 7-day baseline data collection phase, but all results must be confirmed negative prior to randomization.

Patients with a positive screening UDS due to an allowed prescription drug (eg, headache remedies containing butalbital) do not require further drug screening.

Each clinically significant abnormal laboratory value or other clinically meaningful abnormality should be followed until the abnormality resolves or until a decision is made that it is not likely to resolve. If such abnormalities do not return to normal within a reasonable period, their etiology should be identified and Tonix or designee should be notified. Clinically significant abnormalities in laboratory values after the Screening Visit labs will be recorded as AEs.

NOTE: A screening TSH level greater than 1.5 times higher than the upper limit of normal, glycated hemoglobin (HbA1c) > 7.5%, or ALT or AST level > 2 times the upper limit of normal, is exclusionary; however, the patient may remain in screening to undergo repeat liver function assessments if a transient abnormality (eg, viral illness; effects of a medication being discontinued, etc.) is thought to be responsible for their initial elevation.

Table 3: Clinical Laboratory Assessments

Clinical chemistry	**Hematology**
Alanine aminotransferase (ALT/SGPT) [a]	Hematocrit
Alkaline phosphatase	Hemoglobin
Aspartate aminotransferase (AST/SGOT) [a]	Erythrocyte sedimentation rate (ESR) [c]
Bicarbonate	MCH concentration (MCHC)
Bilirubin (direct and total)	Mean corpuscular hemoglobin (MCH)
Blood urea nitrogen (BUN)	Mean corpuscular volume (MCV)
Calcium	Platelet count
Chloride	Red blood cell (RBC) count
Cholesterol (total)	WBC differential
Creatine kinase (CK)	Neutrophil count (absolute and %)
Creatinine	Lymphocyte count (absolute and %)
Glucose	Monocyte count (absolute and %)
Lactate dehydrogenase (LDH)	Eosinophil count (absolute and %)
Phosphorus	Basophil count (absolute and %)
Potassium	White blood cell (WBC) count
Protein (albumin and total)	Red blood cell distribution width (RDW)
Sodium	**Viral testing**
HbA1c [b,c]	Anti-HIV antibodies [c]
Thyroid-stimulating hormone (TSH) [c,d]	Anti-HCV antibodies [c]
Free T4 only if TSH is outside of normal limits	HBsAg [c]
Pharmacogenomic testing (optional; can be obtained at any visit post-Screening, including an Early Termination Visit. However, it is preferred that these samples are collected at Visit 2)	**Other**
	Urinalysis
	Serum Pregnancy Test [c,e]
	Urine Pregnancy Test (qualitative dipstick) [e]
	Urine Drug Screen [f]

[a] Level greater than 2 times the upper limit of normal is an exclusion (if persistent upon repeat).

[b] HbA1c ≥ 7% is exclusionary at Visit 1.

[c] Test performed at Visit 1 only.

[d] TSH level greater than 1.5 times higher than the upper limit of normal is exclusionary at Visit 1.

[e] Pregnancy testing for females of child-bearing potential only. A positive pregnancy test is exclusionary (Visit 1 or Visit 2) or mandates withdrawal from the study (all other visits).

[f] Urine drug screening will be conducted on all patients at Screening and, if necessary, prior to the beginning of the 7-day baseline data collection phase in patients washing off opioids, amphetamines, or benzodiazepines and who otherwise qualify for the study.

12.2.7. Electrocardiogram

A 12-lead ECG will be performed at Visit 1 and reviewed by the Investigator for the purpose of excluding from participation patients who have either a history of or current evidence of clinically significant cardiac disease (eg, significant arrhythmias or heart block, left bundle branch block, heart failure, symptomatic coronary artery disease, myocardial infarction within the preceding 2 years), or a QTcF at Screening > 450 msec if male or 470 msec if female. The ECG interpretation by the Investigator will be recorded in the CRF as normal, abnormal but clinically insignificant, or abnormal and clinically significant. In addition, the standard ECG parameters including rhythm, heart rate, and intervals for RR, QT, PR, QRS, and QTcF (Fridericia's correction) will be recorded.

If the Investigator has any concerns about the eligibility of a patient or wishes to confirm his/her assessment, the Investigator should consult with the Medical Monitor for this study.

12.3. Pharmacogenomic Testing (Optional)

For optional pharmacogenomic analyses, blood samples will be obtained from each patient who provided separate written, signed informed consent for pharmacogenomic analysis. These samples may be obtained at any post-screening visit, including an ET Visit; however, it is preferred that they are collected at Visit 2 whenever possible. The purpose of this testing is to allow for whole genome sequencing (WGS) and analysis for allelic polymorphisms related to treatment response to TNX-102 SL.

Please refer to the Laboratory Manual for additional details on the sample collection methods and materials used in this study.

Unused extracted DNA may be stored up to 15 years and potentially utilized to develop a pharmacogenomic test for determining the likelihood of treatment response to TNX-102 SL. A decision not to participate in optional pharmacogenomic testing will not affect the patient's eligibility for the main study. Patients have the right to stop participating at any time during the study or during the time of sample storage, and, if a patient decides to withdraw from the pharmacogenomics portion of this study, any remaining sample will be destroyed and not used for further research. Data collected before a patient's withdrawal from the pharmacogenomics portion of this study will remain in the research database and included in the Sponsor's analyses and reports.

13. STATISTICAL CONSIDERATIONS AND ANALYSES

A complete description of the statistical analyses to be performed will be provided in the study -specific statistical analysis plan (SAP), which will be finalized prior to database lock and the unblinding of study treatments.

Baseline will be defined as those values recorded closest to, but prior to administration of, the first dose of study drug.

13.1. Populations for Analysis

In the case that the study goes to full enrollment or has a sample size increase, the following analysis populations are planned for this study:

- All Patients: used for summaries of dispositions of patients; tabulations of dispositions may also use the populations below.
- Safety population: all patients who receive at least one dose of the investigational product. All safety analyses will be performed using this population, analyzed as treated.
- Intention-to-treat (ITT) population: all patients who are randomized. This is the primary population for efficacy analyses, and patients will be analyzed based on their randomized treatment.

In the case of an early stop for efficacy or for futility from the interim analysis, the following populations will be utilized:

- All Patients: used for summaries of dispositions of patients; tabulations of dispositions may also use the populations below.
- Interim Safety population: all patients who receive at least one dose of the investigational product and included in the cohort of interim analysis patients. All safety analyses will be performed using this population, analyzed as treated.
- Interim ITT population: all patients who are randomized and included in the cohort of interim analysis patients. This is the primary population for efficacy analyses, and patients will be analyzed based on their randomized treatment.
- Full Safety population: all patients who receive at least one dose of the investigational product. This will be used for supportive safety analyses on all patients exposed in the study, analyzed as treated.

13.2. Estimate of Sample Size

The study is planned to enroll approximately 470 patients total in a 1:1 randomization, 235 patients in each of the TNX-102 SL 5.6 mg and placebo arms. Using a two-sided test with an alpha level of 0.05, a sample size of 235 per group provides a power of at least 90% if the effect size is 0.3.

13.3. Assessment of Demographic and Baseline Characteristics

Demographic and baseline characteristics such as age, gender, race/ethnicity, height, weight, BMI, family status, education, employment status, smoking history, and MINI modules (A, C, I, J, K, O) will be summarized by treatment group (TNX-102 SL and placebo) and overall using descriptive statistics.

Medical History will be coded using the Medical Dictionary for Regulatory Activities (MedDRA)® and summarized by system organ class (SOC) and Preferred Term using frequency counts by treatment group.

13.4. Efficacy Analyses

13.4.1. Primary Efficacy Analysis

The primary efficacy parameter will be the contrast between TNX-102 SL and placebo in the weekly mean change in worst pain score from Baseline to Week 14. The weekly pain score will be based on the weekly average of the daily diary patient self-reported 24-hour recall worst Long COVID pain intensity scores using an 11-point (0−10) NRS. A weekly value will be calculated as long as at least one daily measure is recorded.

The primary ITT analysis will provide the following causal estimand for the primary analysis: the difference in the weekly mean change from Baseline of the daily patient self-reported 24-hour recall worst Long COVID pain intensity rating using an 11-point (0−10) NRS evaluated at the Week 14 endpoint in all randomized patients attributable to the initially randomized treatment assignment.

The primary analysis will use a Mixed Model Repeated Measures (MMRM) approach with multiple imputation (MI) for missing data. Covariates in the model will include the fixed categorical effects of treatment, pooled site (with small sites pooled into a single large site), study week, and treatment by study week interaction, as well as the continuous fixed covariates of baseline score and baseline score by study week interaction. An unstructured covariance structure will be used to model the within-patient errors. If this analysis fails to converge, the following structures will be tested in this order: first order ante dependence, heterogeneous first order autoregressive, heterogeneous compound symmetry, and compound symmetry with the first to give convergence used. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom (DDFM) with the unstructured matrix; other covariance structures will utilize the sandwich matrix and the Statistical Analysis System (SAS) default DDFM. The least square (LS) means and differences across the 20 MI repeats will be combined using SAS procedure MIANALYZE (Rubin, 1976). Significance testing will be based on least-squares means and two-sided 95% confidence intervals will be presented. The p-values will be compared against a two-sided alpha of 0.046.

13.4.2. Missing Data Imputation

For individual daily pain scores, since a mean is used in the calculation of the primary endpoint, it is not necessary to replace values missing on random intermittent days; weeks will have average values as long as a single value for that week is present.

[redacted]

13.5. Sensitivity Analyses

The primary analysis will be followed by several sensitivity analyses. The SAP will include full details of the sensitivity analyses planned for this study.

13.6. Secondary Efficacy Analyses

Secondary efficacy analyses will be based on the ITT population. For the purposes of possible label claims and reported p-values entered into the multiplicity algorithm, an approach identical to the primary analysis will be used for all key secondary continuous outcomes.

Analyses of other continuous secondary endpoints will be similar to the analysis of the primary endpoint, utilizing MMRM, but without MI for missing data. Significance tests of treatment

differences will be based on least-squares means, and corresponding 95% confidence intervals will be calculated.

A categorical analysis of PGIC will compare the treatment arms with a difference in proportions Z test (equivalent to a Pearson's Chi Squared). Subjects with results of "very much improved" or "much improved" (defined as responders) will be compared to all other categories (defined as non-responders). Subjects with missing data will be considered non-responders. The percentages of responders and the 95% CIs of the percentages as well as the difference in the percentages and its 95% CI will be reported. A summary of frequency counts for all PGIC responses for each time point will be presented; Week 14 is of primary interest and all other time points are considered exploratory.

To adjust for multiplicity and to control for overall type I error, a sequential test procedure will be applied to the primary and key secondary efficacy endpoints. If the primary analysis produces a result that is statistically significant at the two-sided 0.046 level, a significance level of 0.046 will be used for comparing the key secondary endpoints in an ordered fashion. If the analysis for a key secondary endpoint does not produce a statistically significant result at the 0.046 level, then the remaining key secondary endpoint analyses will automatically be considered non-significant regardless of the p-value produced. In the case of an early stop for efficacy, this will be the same as the stopping criteria for the primary efficacy endpoint (secondary endpoints will be tested at p-value = 0.005, one-sided).

The order in which the key secondary endpoints are to be tested will be specified in the SAP.

No other adjustments for multiplicity will be made, and other p-values displayed in the output will be considered for descriptive summary purposes only and will not be used for formal inference. Full details regarding the statistical analyses for the listed endpoints, including graphical presentations, can be found in the SAP.

13.6.1. Exploratory Efficacy Analyses

Exploratory efficacy analyses will be based on the ITT population. Details on exploratory efficacy analyses can be found in the SAP.

13.7. Safety Analyses

Safety analyses will be performed using the Safety Population. The analysis of safety assessments in this study will include summaries of the following safety and tolerability data collected for each patient:

- Incidence of AEs
- Changes from Baseline in clinical laboratory tests
- Changes from Baseline in vital signs
- Changes from Baseline in physical examination findings including examination of the oral cavity
- Monitoring suicidality using the C-SSRS

All AEs, treatment-emergent adverse events (TEAEs), and SAEs will be coded using the MedDRA.

An AE summary table will be presented for the following:

- All TEAEs
- TEAEs by severity
- TEAEs leading to study drug discontinuation
- TEAEs by relationship
- SAEs
- Oral cavity TEAEs
- Oral cavity TEAEs by severity

Summaries of incidence rates (frequencies and percentages), of individual AEs by MedDRA SOC and preferred term will be prepared. Such summaries will be displayed for all TEAEs, oral cavity TEAEs, TEAEs by maximum severity, and TEAEs by strongest relationship to study drug.

Each patient will be counted only once within each summation level (SOC; preferred term). If a patient experiences more than one TEAE within each summation level, the TEAE with the strongest relationship or the maximum severity, as appropriate, will be included in the summaries of relationship and severity.

In the AE data listings, all AEs will be displayed.

Laboratory data include analytes for chemistry and hematology, and these will be summarized by treatment and visit for the Safety Population. Descriptive summaries of actual values and changes from Baseline will be presented by study visit and last available assessment for each clinical laboratory analyte and each treatment group. 95% confidence intervals will be presented for change from Baseline.

Laboratory values will be displayed in the data listings with their corresponding normal ranges, and those values that are outside the normal range will be flagged. For each laboratory analyte, shifts in assessments of abnormality from Baseline to each scheduled time point will be presented in shift tables.

A by-patient listing of all clinical laboratory data will also be provided.

Descriptive summaries (n, mean, standard deviation, median, range, minimum, and maximum) of actual values and changes from Baseline at each assessment time point and last-available assessment will be calculated for vital signs including weight, BMI, body temperature, pulse rate, systolic blood pressure, and diastolic blood pressure. Ninety-five- percent confidence intervals will be presented for change from Baseline.

Based on the C-SSRS results, the overall number of patients with lifetime and/or current suicidal ideation (by item and category), suicidal behavior (by item and category), or self-injurious behavior at the Screening and Baseline Visits will be summarized by visit and treatment group. Additionally, the number of subjects with increase over baseline in suicidal ideation at any time

point will be reported. The maximum ideation across all visits for a subject will also be summarized with counts and percentages both for all subjects and among subjects with an increase in ideation. Likewise, the count and percentage of subjects with any suicidal behavior will be reported along with a summary of the most extreme behavior each subject reported.

Physical examination data and oral examination data will be presented in data listings.

13.8. Interim Analyses

An interim analysis will be performed when approximately 50% of the initially planned enrollment is evaluable for efficacy assessments. This interim analysis will be performed by an unblinded team separate from the team responsible for the conduct and analysis of the study. An Independent Data Monitoring Committee (IDMC) will review the data and recommend to the Sponsor one of the following:

- Stop the study early for efficacy if the one-sided alpha for the primary endpoint is less than 0.005
- Increase the sample size by a fixed amount
- Keep the current sample size and continue as planned
- Stop the study early for futility if conditional power at interim is <20%

The recommendations are nonbinding, and the Sponsor may make adjustments other than those detailed above; however, the Sponsor will receive no information other than the recommendations listed.

These assessments will be based on the primary analysis of the primary outcome; however, the committee will have additional outputs such as demographics, dispositions, and other key efficacy analyses. If the p-value for the primary falls short of stopping for efficacy, but the conditional power (CP) based on this is still greater than 90%, then the IDMC will recommend no change in sample size. If the conditional power is less than 90% but greater than or equal to 20% the IDMC will recommend an increase in sample size, with the maximum increase limited to 220 additional subjects and any increase done in blocks of 20 subjects. The increase will be chosen with the goal of increasing the sample size by the minimum number of subjects sufficient to raise the conditional power to at least 90%. If the 220 subject increase is insufficient to increase the power over 90%, an increase of 220 patients will be recommended as long as the CP at the original planned sample size of 470 patients is over 20%. If the CP is below 20%, then the recommendation will be to halt the study for futility. No further information will be provided to the sponsor beyond this recommendation.

The interim analysis will be conducted approximately 18 weeks after randomization of approximately 235 participants, i.e. when approximately 50% of the initially planned participant enrollment (470) is evaluable for efficacy assessments (approximately 14 weeks); and related data cleaning, database freeze, and administrative tasks have been completed on this cohort (approximately 4 weeks).

In the case of an early stop for efficacy or futility, all ongoing subjects will be asked to return to the clinic and complete an early termination visit, and the study will be halted once all subjects have completed their termination visit.

13.8.1. P-value Adjustment for the Interim Analysis

The interim analysis will test the primary and key secondary outcomes at the one-sided alpha=0.005 for the purposes of an early stop for efficacy; if the study is not stopped, the corresponding final alpha level to account for the first stage alpha spend (should the study continue to full enrollment) will be 0.046 (two-sided). For simplicity, 95% confidence intervals will be reported throughout, but for the purposes of study success, label claims and multiplicity, p-values will be compared to 0.046.

Data from the interim and post-interim cohorts will be combined using the inverse normal method (Cui et al. 1999):

$$Z_1 = \Phi^{-1}(1 - p_1)$$
$$\text{and } Z_2 = w_1 Z_1 + w_2 \Phi^{-1}(1 - p_2) \qquad (1)$$

where:

Z_1 = the Z statistic for the first stage
Z_2 = the combination test statistic at the end of the second stage
w_i = the weighting applied for each associated Z statistic

p_1 = the first stage p-valuep_2 = the second stage p-value based on the second stage participants The weights are defined prospectively according to the square-root of the planned proportion of participants in the two stages, relative to the preplanned total enrollment of 470 participants, as $wi = \sqrt{0.5}$. To control the type I error, adaptive changes of the stage wise sample sizes will not lead to changes of the weights (Lehmacher and Wassmer. 1999).

Full details of the interim analysis will be included in the SAP and/or IDMC Charter which will be finalized prior to execution of the interim analysis.

14. DEFINITIONS, RECORDING, AND REPORTING OF ADVERSE EVENTS

14.1. Definition of Adverse Events

According to International Council for Harmonisation (ICH) guidance E2A, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, an AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which is not necessarily required to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

A TEAE is an AE that either commenced following initiation of study treatment or was present prior to study treatment but increased in frequency or severity following initiation of study treatment.

14.2. Adverse Event Recording

14.2.1. Coding the Adverse Event

Standard medical terminology should be used in describing AEs. MedDRA v24.1 and WHODRUG Global (B3 format) will be used as the standard coding dictionary for AEs and in describing the patient's medical history, and the WHO Drug Dictionary will be used to code concomitant medications. Informal descriptions should be avoided.

14.2.2. Severity of Adverse Event

AEs should be graded as mild, moderate, or severe using the following definitions.

- ***Mild:*** Awareness of signs or symptoms, but easily tolerated and of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- ***Moderate:*** Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.
- ***Severe:*** Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.

To make sure there is no confusion or misunderstanding of the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, maybe of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

14.2.3. Relationship of Adverse Events to Study Drug

The Investigator will assess the potential relationship of the AE to study drug using the following descriptions.

- ***Not Related:*** This category applies to an AE that is clearly not related to the study drug beyond a reasonable doubt. That is, another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the administration of study drug and/or a causal relationship is considered biologically implausible.
- ***Unlikely Related:*** This category applies to an AE that could reasonably be considered caused by something else, and where there is no known or expected response pattern to the suspected study drug.
- ***Possibly Related:*** This category applies to an AE that follows a reasonable temporal sequence from administration of the study drug and that follows a known or expected response pattern to the suspected study drug, but that could readily have been produced by a number of other factors.

14.3. Serious Adverse Events (SAEs) and Serious Adverse Drug Reactions

Any SAE that occurs at any time during the study, including a clinically significantly abnormal laboratory test result that is considered serious, must be reported to Tonix or its designee(s) so that Tonix may comply with regulatory obligations. If the SAE is life-threatening or fatal, it must be reported to Tonix or its designee(s) immediately, by facsimile and telephone. For these and all other SAEs, an SAE report form must be completed and sent by facsimile or email to Tonix or its designee(s) within 1 working day of the site's initial awareness of the event. These requirements apply equally to all patients, regardless of the study phase or the at-risk patient's treatment assignment or dosage.

An SAE (experience) or reaction is any untoward medical occurrence that, at any dose:

- Results in death,
- Is life-threatening,
- Requires in-patient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or
- Is an important medical event.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately

life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. *These should also usually be considered serious.* Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. The development of C-SSRS suicidal ideation type 4 (intent) or type 5 (specific plan and intent) any time after consenting to the study should always be reported as an SAE. Additionally, since only Types 1 and 2 are allowed at Screening or Baseline, the development of C-SSRS Type 3 (method but no plan or intent) after consenting should always be reported as an AE.

Any death occurring during the study, during the per-protocol follow-up period, or reported to the Investigator after study participation (no required post-study time limit) must be reported to Tonix or its designee(s) immediately, whether or not it is considered treatment-related. Initial SAE reports must be followed by detailed descriptions. These should include copies of hospital case records and other documents when requested. Telephone reports must be confirmed promptly either by facsimile or by e-mail. For reporting SAEs, Tonix's designated Medical Monitor should be called, and the relevant forms submitted to Premier pharmacovigilance within 24 hours of the site's awareness of the SAE. The contact information for the Medical Monitors is as follows:

The Investigator, or the Sponsor or designee in the case of a central institutional review board (IRB), also must notify the ethics committee (EC)/IRB of the occurrence of the SAE, in writing, as soon as is practicable and in accordance with local law. A copy of this notification must be provided to Tonix or its designee.

In the event of an SAE that meets the criteria for expedited reporting, an investigational new drug (IND) Safety Report will be prepared for submission to the FDA.

Clinical investigators also have the authority to unblind their own SAE patients if/when the unblinded treatment information could impact the patient's clinical management. There is a module within the IRT system for investigators' use if "emergency" unblinding is required; however, the Investigator is requested to confer with the Medical Monitor before taking any action. The need for emergency unblinding is not expected for this study, in light of the nature of the study drug.

14.4. Pregnancy

The active pharmaceutical product in TNX-102 SL is cyclobenzaprine HCl, which is in Pregnancy Category B (AMRIX® Package Insert, 2020). All pregnancies occurring during the study (after exposure to study drug) or within 28 days after discontinuation of study drug must be followed until resolution (ie, birth or voluntary or spontaneous termination of the pregnancy). All women of childbearing potential are therefore required to continue contraception for 28 days after study drug discontinuation. Any patient found to be pregnant at any time during the study will be withdrawn from the study immediately. Any pregnancy outcome that meets the criteria for an SAE will be reported as an SAE.

15. PROCEDURES FOR MODIFYING THE PROTOCOL OR TERMINATING THE STUDY

15.1. Protocol Modifications and Deviations

The Investigator will make all reasonable efforts to comply with the written protocol and protocol amendments. All protocol modifications must be reviewed and approved by the appropriate EC/IRB before the revised protocol can be implemented. Emergency revisions that eliminate an apparent hazard to patients do not require preapproval by the EC/IRB. However, the EC/IRB must be notified, in writing, as soon as possible after the modification has been made. A copy of this communication must be forwarded to Tonix.

15.2. Study Termination

The study may be prematurely terminated at any time at the discretion of Tonix, its designee, or the Principal Investigator. Should premature termination be considered necessary, written notification documenting the reason for study termination will be provided, and specific procedures for termination will be arranged. Circumstances that may warrant premature study termination include, but are not limited to, the following:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enroll patients at an acceptable rate
- Insufficient adherence to the requirements of the protocol
- Insufficient provision of complete and evaluable data
- Plans to modify, suspend, or discontinue development of the study drug

In the event that the study is terminated prematurely, all study materials must be returned to Tonix or its designee.

16. ETHICAL CONSIDERATIONS

16.1. Ethical Conduct of the Study

This protocol is written in accordance with the principles established by the 18th World Medical Assembly General Assembly (Helsinki, 1964) and amendments and clarifications adopted by subsequent General Assemblies. The Investigator will make sure that the study described in this protocol is conducted in full conformance with those principles, the protocol, current FDA regulations, ICH Good Clinical Practices (GCP) guidelines, Good Laboratory Practices (GLP) guidelines, local ethical and regulatory requirements, including the Federal Food, Drug and Cosmetic Act, US applicable Code of Federal Regulations (title 21), and any EC/IRB requirements relative to clinical studies. As required by the US FDA, the study drug may not be shipped to any participating Investigator until the requisite study documentation has been submitted to the IND.

Should a conflict arise, the Investigator will follow whichever law or guideline affords the greater protection to the individual patient. The Investigator will also make sure he or she is thoroughly familiar with the appropriate administration and potential risks of administration of the study drug, as described in this protocol and the Investigator's Brochure, prior to the initiation of the study.

16.2. Ethics Committee/Institutional Review Board (EC/IRB) Review

The EC/IRB must be a properly constituted board or committee operating in accordance with 21 CFR Part 56, "Institutional Review Boards." This protocol, any protocol amendments, the associated ICFs, and the informed consent procedures must be submitted to the EC/IRB for review and approved before the enrollment of any patient into the trial.

All types of patient recruitment or advertising information must be submitted to Tonix or its designee and to the EC/IRB for review and approval prior to implementation. EC/IRB approval of any protocol amendments must be received before any of the changes outlined in the amendments are put into effect, except when the amendment has been enacted to eliminate a potential hazard to study patients. In such cases, the chair of the EC/IRB should be notified immediately and the amendment forwarded to the EC/IRB for review and approval.

16.3. Written Informed Consent

It is the responsibility of the Investigator to obtain signed written informed consent from each potential study patient prior to the conduct of any screening or other study procedures. This written informed consent will be obtained after the methods, objectives, and potential risks of the study have been fully explained to the potential patient. The Investigator must explain to each patient that he or she is completely free to refuse to enter the study or to withdraw from it at any time. NOTE: Patients on antidepressant therapy should be warned of a potential serious drug interaction and should be advised to contact their study site immediately if they experience any symptoms that might represent possible serotonin syndrome, including fever, confusion or agitation, hallucinations, sweating, high or low blood pressure, rapid heart rate, tremor, muscle rigidity, or nausea, vomiting, or diarrhea.

The patient should also be asked in the ICF for permission for the Principal Investigator or his designee to contact the patient's other personal physicians, as appropriate, concerning participation in the study.

The method of obtaining and documenting informed consent and the contents of the ICF will comply with ICH GCP guidelines, the requirements of 21 CFR Part 50, "Protection of Human Patients," the Health Insurance Portability and Accountability Act (HIPAA) regulations, and all other applicable regulatory requirements. A properly executed written ICF shall be read, signed, and dated by each patient prior to entering the trial or prior to performing any study procedure. The original signed and dated ICF will be kept on file at the study site. Patients will be given a copy of the signed ICF and will be informed of any new developments during the course of the study that might influence their continued participation in the study.

The Investigator or a qualified designee will be available to answer each patient's questions throughout the study, and all questions must be answered to the patient's satisfaction. If the protocol is amended and a revised ICF is introduced during the study, each patient's further consent must be obtained. The new version of the ICF must be approved by the EC/IRB, prior to subsequently obtaining each patient's consent.

Receipt of written informed consent will be documented in each patient's or potential patient's CRF. The signed ICF must remain in each patient's study file and must be available for verification by study monitors at all times.

Separate written, signed informed consent must be obtained if the patient is to participate in the optional pharmacogenomic assessment.

17. DATA HANDLING, RECORD KEEPING, MONITORING AND AUDITS

17.1. Maintaining Privacy and Confidentiality

In order to maintain patient privacy, all CRFs, study drug accountability records, and other documents, including communications between the study site and Tonix, will identify patients only by their initials and their assigned study identification numbers. If required, the Investigator will grant monitors and auditors from Tonix or its designee and/or regulatory authority's access to patients' original medical records for verification of the data gathered on the CRFs and to audit the data collection process. Patients' confidentiality will be maintained, and patient information will not be made publicly available unless mandated by applicable laws and regulations.

17.2. Maintaining Essential Clinical Documents

Study site files for the retention of regulatory documents will be established at the beginning of the study, maintained for the duration of the study, and retained according to FDA and ICH/GCP guidelines and applicable regulatory requirements. The records maintained must be adequate to fully document appropriate protection of study patients/patients, the validity of the study, the integrity of the data, and the manner in which the study was conducted.

The Investigator's site file, copies of protocols, CRFs, originals of test result reports, drug disposition logs, correspondence, records of written informed consent, and other documents pertaining to the conduct of the study must be kept on file by the Investigator and in readily accessible order for at least 2 years after the last approval of a marketing application, until at least 2 years have elapsed after formal discontinuation of the clinical development of the investigational product, or according to local regulatory requirements. No study document may be destroyed without prior written consent from Tonix or its designee. Should the Investigator wish to withdraw from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. Tonix must be notified in writing in advance if a custodial change is to occur. It is important that the Investigator remain ready to provide background information from the archived study records on request.

The Sponsor or designee will maintain adequate study records for at least 2 years after the last approval of a marketing application or for at least 2 years after clinical development of the study drug for the indication being studied has been discontinued. After that period, the sponsor will be contacted to determine whether the study records will be forwarded to the sponsor, destroyed, or kept at the location of the designee or another facility for a longer period of time.

17.3. Data Handling

Unless otherwise specified, procedures, data collection and evaluation will be conducted as per the Standard Operating Procedures of the contract research organization (CRO). The Investigator will assume the responsibility of ensuring the completeness and accuracy of the clinical data. All data will be verified for quality control and will also be patient to audits from Tonix or designee to ensure quality.

All laboratory results will be analyzed by an accredited and licensed clinical laboratory facility. Clinical laboratory data will be transferred from the central laboratory to the clinical database maintained by the CRO using systems that are validated and Part 11-compliant.

The responsible clinical study monitor(s) will check data at the monitoring visits to the clinical study site. The Investigator will ensure that the data collected are accurate, complete, and legible. Any changes made to the clinical data will be documented with a full audit trail.

Aspects of the clinical and statistical phases of the study, including all associated documentation, may be reviewed by the Quality Assurance Unit of the CRO using a risk-assessment approach. The final clinical and statistical report will be audited to ensure that, as far as can be reasonably established, the methods described and the results reported accurately reflect the raw data generated during the study.

17.4. Case Report Forms (CRFs)

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study patient. Data must be recorded on CRFs approved by Tonix or its designee. Data (including AEs) will be recorded on raw data sheets and/or electronic or paper source documents.

If selected data are collected via paper (patient questionnaires, etc.), the data must be entered into the CRF and verified that it has been transcribed correctly.

17.5. Clinical Laboratory Certification

A central clinical laboratory will be used to analyze all samples in this study, with the exception of the post-Screening urine pregnancy tests and ad hoc urine drug screens. The Investigator must maintain, on file, written evidence that the central clinical laboratory to be used is certified under the Clinical Laboratory Improvement Act or equivalent certification (depending on local regulations). Further, the Investigator will maintain a copy of the certification, the range of normal values, the effective dates for the ranges, and the units of measurement for all laboratory tests requested in the protocol. If any of the laboratory measurements will be transformed and/or categorized in any way, a description of the procedures(s) used should be included. The Investigator is expected to receive these documents before the shipment of clinical supplies.

17.6. Site Monitoring and Tonix's Right to Review Records

Monitoring and auditing procedures developed by Tonix and/or its designee will be implemented to ensure compliance with FDA and ICH GCP and GLP guidelines.

Tonix's designated representative (the monitor or auditor) will contact the Investigator and conduct regular visits to the clinical site. In extenuating circumstances related to the COVID-19 pandemic, remote monitoring will be permissible. The monitor will be expected and allowed to verify the Investigator's qualifications, to inspect clinical site facilities, and to inspect study records, including proof of EC/IRB review, with the stipulation that patient confidentiality will be maintained in accordance with local and federal regulations, including HIPAA requirements. The monitor will also be responsible for confirming adherence to the study protocol, inspecting CRFs and source documents, and ensuring the integrity of the data. CRFs will be checked for accuracy, completeness, and clarity and will be cross-checked for consistency with source

documents, including laboratory test reports and other patient records. Instances of missing or uninterpretable data will be resolved in coordination with the Investigator.

The monitor/auditor will also investigate any questions concerning adherence to regulatory requirements. Any administrative concerns will be clarified and followed. The monitor will maintain contact with the site through frequent direct communications with the study site by e-mail, telephone, facsimile, and mail. The Investigator and all other site personnel agree to cooperate fully with the monitor and will work in good faith with the monitor to resolve any and all questions raised and difficulties detected by the monitor.

17.7. Audits and Inspections

The Investigator understands that regulatory authorities, the EC/IRB, and/or Tonix or their designees have the right to access all CRFs, source documents, and other study documentation for on-site audit or inspection and will retain this right from the start of the study to at least 2 years after the last approval of a marketing application or for at least 2 years after clinical development of the study drug for the indication being studied has been discontinued. The Investigator is required to guarantee access to these documents and to cooperate with and support such audits and inspections.

18. CONFIDENTIALITY

18.1. Protection of Patient Anonymity

The Investigator must make sure that each patient's anonymity is maintained. On CRFs or other documents submitted to Tonix or its agent, patients should not be identified by their names, but rather by their initials and the assigned study identification numbers. The Investigator should keep a separate record of the patient initials, randomization codes, patient names, address, and contact information. Documents that contain the names associated with these initials and codes are not for submission to Tonix or its agents (eg, written ICFs). These records should be maintained by the Investigator in strict confidence except to the extent necessary to allow auditing by regulatory authorities, Tonix, or its agents. These records should be kept in compliance with HIPAA regulations.

18.2. Confidentiality of Study Information

All information relevant to this study, whether supplied by Tonix or its agents to the Investigator or collected by the Investigator in support of this study, is privileged and confidential. The Investigator agrees to use this information to carry out the study and will not use it for other purposes without written consent from Tonix. It is understood that the Investigator is under obligation to provide Tonix with all data obtained during the study. The information obtained from this study will be used by Tonix toward the clinical development of the indicated investigational drug and may be disclosed by Tonix to regulatory authorities, other Investigators, corporate partners, or consultants as required.

18.3. Publication of Data and Protection of Trade Secrets

No presentations, abstracts (including meeting abstracts), or other publications based on the conduct or results of this study will be permitted without the express written permission of Tonix or its designated agent. All such presentations or publications will proceed only as collaborations between Tonix and the Investigators.

If the Investigator wishes to publish the results of this study, a copy of the proposed manuscript or abstract (including meeting abstracts) will be provided to Tonix or its designee for review, revision, and approval at least 60 days before the expected date of submission for publication, unless otherwise arranged with Tonix in writing. This will enable Tonix to protect its proprietary information and augment the publication with insights or information of which the Investigator may not be aware.

Patient names and other identifiers, such as photographs or audio or video recordings, may not be disclosed in any publication or public forum without prior written authorization from the patients involved or their legal guardians.

19. REFERENCES

Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature.* 2021;594(7862):259-64.

Bierle DM, Aakre1 CA, Grach SL, et al. Central Sensitization Phenotypes in Post Acute Sequelae of SARS-CoV-2 Infection (PASC): Defining the Post COVID Syndrome. *J Prim Care Community Health*. 2021;12:1-8.

Brummett CM, Goesling J, Tsodikov A, Meraj TS, Wasserman RA, Clauw DJ, Hassett AL. Prevalence of the fibromyalgia phenotype in patients with spine pain presenting to a tertiary care pain clinic and the potential treatment implications. *Arthritis Rheum*. 2013;65(12):3285-92.

Brummett CM, Janda AM, Schueller CM, Tsodikov A, Morris M, Williams DA, Clauw DJ. Survey Criteria for Fibromyalgia Independently Predict Increased Postoperative Opioid Consumption after Lower-extremity Joint Arthroplasty: A Prospective, Observational Cohort Study. *Anesthesiology*. 2013;119(6):1434-43.

Brummett CM, Urquhart AG, Hassett AL, Tsodikov A, Hallstrom BR, Wood NI, Williams DA, Clauw DJ. Characteristics of fibromyalgia independently predict poorer long-term analgesic outcomes following total knee and hip arthroplasty. *Arthritis Rheumatol*. 2015;67(5):1386-94.

Brummett CM, Lohse AG, Tsodikov A, Moser SE, Meraj TS, Goesling J, Hooten M, Hassett AL. Aberrant analgesic response to medial branch blocks in patients with characteristics of fibromyalgia. *Reg Anesth Pain Med*. 2015;40(3):249-54.

Brummett CM, Bakshi RR, Goesling J, et al. Preliminary validation of the Michigan Body Map. *Pain.* 2016;157(6):1205-12.

Chopra V, Flanders SA, O'Malley M. Sixty-day outcomes among patients hospitalized with COVID-19. *Ann Intern Med.* 2020;174(4):576-8.

Clauw DJ, Hauser W, Cohen SP, Fitzcharles MA. Considering the potential for an increase in chronic pain after the COVID-19 pandemic. *Pain.* 2020;161(8):1694-7.

Crook H, Raza S, Nowell R, et al. Long COVID – Mechanisms, risk factors, and management. *BMJ.* 2021;374:n1648.

Cui L, Hung HMJ, Wang SJ. Modification of sample size in group sequential clinical trials. *Biometrics*. 1999 Sep;55:853-857.

Davis HE, Assaf GS, McCorkell L, et al. Characterizing Long COVID in an International Cohort: 7 Months of Symptoms and Their Impact. *EClinicalMedicine.* 2021;38:101019.

Dworkin RH, Turk DC, Wyrwich, KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain*. 2008;9:105-21.

Fitzcharles MA, Cohen SP, Clauw DJ, et al. Nociplastic pain: towards an understanding of prevalent pain conditions. *Lancet.* 2021;397:2098-110.

Gagnier JJ, Bergmans RS, Clauw DJ. Musculoskeletal Components of Post-Acute Sequelae of SARS-CoV-2 Infections. *Submitted*.

Goesling J, Moser SE, Zaidi B, et al. Trends and predictors of opioid use after total knee and total hip arthroplasty. *Pain.* 2016;157(6):1259-65.

Guy W. ECDEU assessment manual for psychopharmacology (DHEW Publication No. ADM 76-338). Washington, DC, U.S. Government Printing Office, 1976.

Hassett AL, Wasserman R, Goesling J, Rakovitis K, Shi B, Brummett CM. Longitudinal assessment of pain outcomes in the clinical setting: development of the "APOLO" electronic data capture system. *Reg Anesth Pain Med*. 2012;37(4):398-402.

Hassett AL, Hilliard PE, Goesling J, Clauw DJ, Harte SE, Brummett CM. Reports of chronic pain in childhood and adolescence among patients at a tertiary care pain clinic. *J Pain*. 2013;14(11):1390-7.

Hassett AL, Pierce J, Goesling J, et al. Initial validation of the electronic form of the Michigan Body Map. *Reg Anesth Pain Med.* 2019;rapm-2019-101084.

Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet.* 2021;397(10270):220-32.

Janda AM, As-Sanie S, Rajala B, Tsodikov A, Moser SE, Clauw DJ, Brummett CM. Fibromyalgia survey criteria are associated with increased postoperative opioid consumption in women undergoing hysterectomy. *Anesthesiology*. 2015;122(5):1103-11.

Johns M.W. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep.* 1991;14(6):540-5.

Klok FA, Boon GJAM, Barco S, et al. The Post-COVID-19 Functional Status scale: a tool to measure functional status over time after COVID-19. *Eur Respir J.* 2020;56(1):2001494.

Kosek E, Clauw D, Nijs J, et al. Chronic nociplastic pain affecting the musculoskeletal system: clinical criteria and grading system. *Pain*. 2021 Nov;162(11):2629-34.

Kratz AL, Whibley D, Alschuler KN, et al. Characterizing chronic pain phenotypes in multiple sclerosis: a nationwide survey study. *Pain*. 2021;162(5):1426-33.

Lambert N, El-Azab SA, Ramrakhiani NS, et al. COVID-19 Survivors' Reports of the Timing, Duration, and Health Impacts of Post-Acute Sequelae of SARS-CoV-2 (PASC) Infection. *medRxiv*. 2021.

Larkin TE, Kaplan CM, Schrepf A, et al. Altered network architecture of functional brain communities in chronic nociplastic pain. *Neuroimage*. 2021;226:117504.

Lawrence J, Hung HMJ. Estimation and confidence intervals after adjusting the maximum information. Biometrical Journal. 2003; 45(2):143-52.

Lehmacher W, Wassmer G. Adaptive sample size calculations in group sequential trials. Biometrics. 1999; 55:1286-90.

Lopez-Leon S, Wegman-Ostrosky T, Perelman C, et al. More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis. *medRxiv.* 2021.

Machado FVC, Meys R, Delbressine JM, et al. Construct validity of the Post-COVID-19 Functional Status Scale in adult subjects with COVID-19. *Health Qual Life Outcomes*. 2021;19:40.

Mease P, Arnold LM, Choy EH, et al. Fibromyalgia syndrome module at OMERACT 9: domain construct. *J Rheumatol.* 2009;36(10):2318-29.

Mehta CR, Pocock SJ. Adaptive increase in sample size when interim results are promising: a practical guide with examples. *Statist Med*. 2011;30:3267–3284.

Minhas D, Clauw DJ. Pain Mechanisms in Patients with Rheumatic Diseases. *Rheum Dis Clin North Am*. 2021;47(2):133-148.

Morin CM, Belleville G, Bélanger L, Ivers H. The Insomnia Severity Index: Psychometric Indicators to Detect Insomnia Cases and Evaluate Treatment Response. *Sleep*. 2011;34(5):601-8.

Nalbandian VA, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. *Nat Med.* 2021;27(4):601-15.

Perrot S, Russell IJ. More ubiquitous effects from non-pharmacologic than from pharmacologic treatments for fibromyalgia syndrome: a meta-analysis examining six core symptoms. *Eur J Pain.* 2014;18(8):1067-80.

Prescribing Information for AMRIX, Dated May 2020.

Prescribing Information for FLEXERIL, Dated April 2013 (Discontinued May 2013).

Raveendran AV, Jayadevan R, Sashidharan S. Long COVID: An overview. *Diabetes Metab Syndr.* 2021;5:869-75.

Rubin DB. Inference and Missing Data. *Biometrika*. 1976; 63:581-92.

Spielman AJ, Saskin P, Thorpy MJ. Treatment of chronic insomnia by restriction of time in bed. *Sleep*. 1987;10(1):45-56.

Sudre CH, Murray B, Varsavsky T, et al. Attributes and predictors of long COVID. *Nat Med.* 2021;27(4):626-31.

Taquet M, Dercon Q, Luciano S, et al. Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19. *PLoS Med.* 2021; 18(9):e1003773.

Ursini F, Ciaffi J, Mancarella L, et al. Fibromyalgia: a new facet of the post-COVID-19 syndrome spectrum? Results from a web-based survey. *RMD Open*. 2021;7:e001735.

Wasserman RA, Brummett CM, Goesling J, Tsodikov A, Hassett AL. Characteristics of chronic pain patients who take opioids and persistently report high pain intensity. *Reg Anesth Pain Med*. 2014; 39(1):13-7.

Williams JBW. Mental health status, functioning and disabilities measures. In: American Psychiatric Association Task Force, editor. *Handbook of Psychiatric Measures.* Washington, DC, USA: American Psychiatric Association; 2000.

Wolfe F, Clauw DJ, Fitzcharles MA, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken). 2010;62(5):600-10.

Wolfe F, Clauw DJ, Fitzcharles MA, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: A modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. J Rheumatol. 2011;38(6):1113-22.

World Health Organisation (WHO) Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis.* 2020;20(8):e192-7.

World Health Organisation (WHO). A clinical case definition of post COVID-19 condition by a Delphi consensus. 6 October 2021. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1

20. APPENDICES

Appendix 1: WHO COVID-19 8-Category Ordinal Scale of Disease Severity

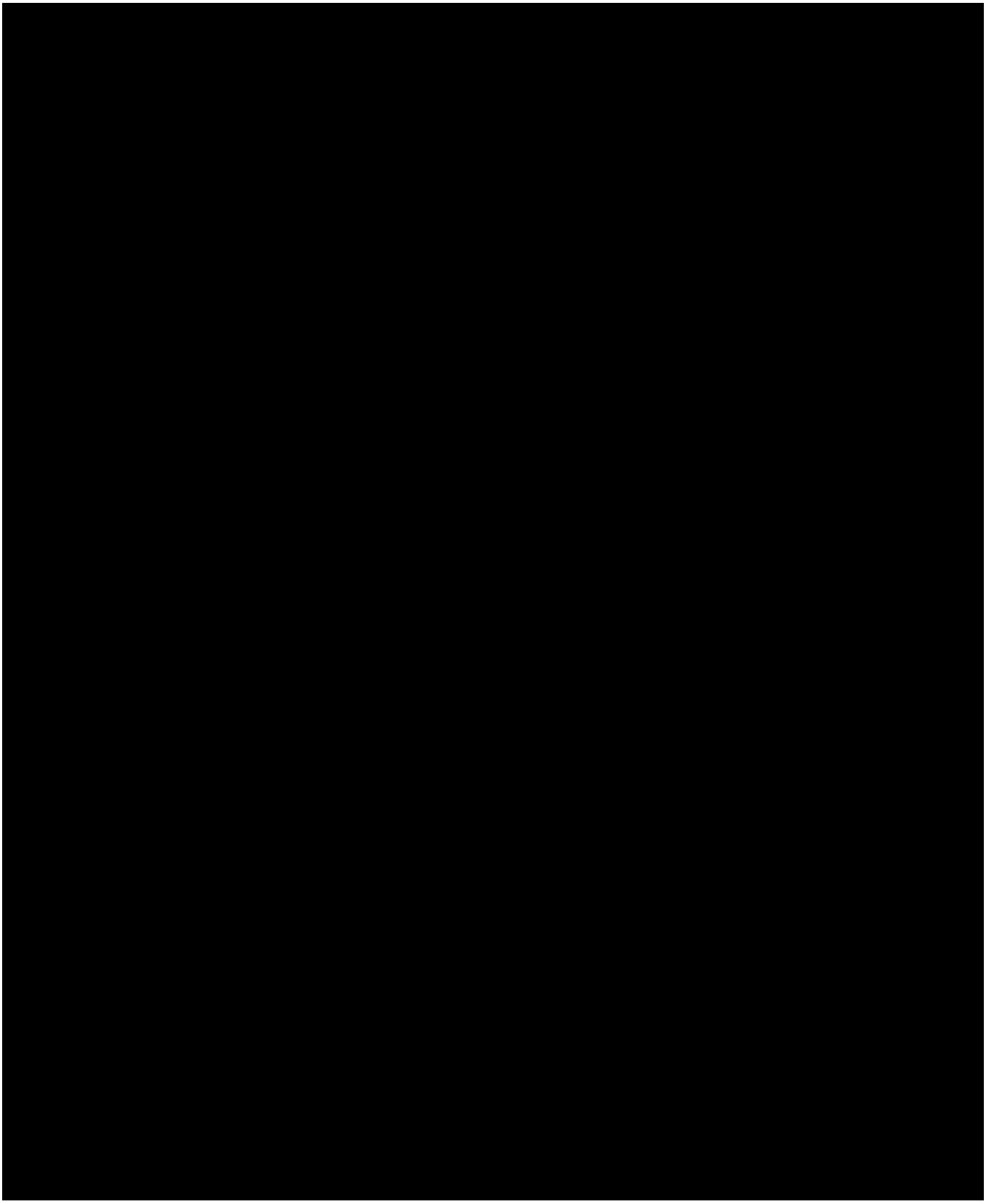
(Reference: WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis.* 2020;20(8):e192-7.)

Value	Status
1	Not hospitalized, no limitation on activities
2	Not hospitalized, limitation on activities and/or requiring home oxygen
3	Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care
4	Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise)
5	Hospitalized, requiring supplemental oxygen
6	Hospitalized, on non-invasive ventilation or high flow oxygen devices
7	Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
8	Death

[redacted]

Appendix 2: Modified Michigan Body Map (mMBM) (Brummett et al. 2015a)

[redacted]

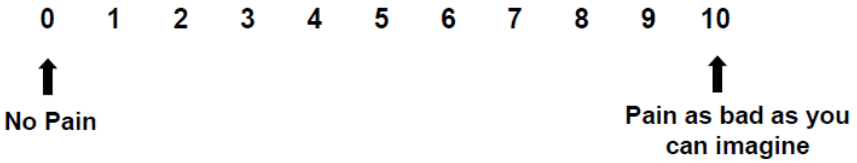


Appendix 3: In-clinic assessment of average daily Long COVID Pain (7-day recall)

Numerical Rating Scale 7-day Pain Recall	**PROTOCOL NUMBER TNX-CY-PA201**	Screening Visit 1
	Patient ID ___ ___ ___ ___ ___ ___ ___	Date

To be completed by the patient. Circle a number.

Rate your <u>average</u> daily Long COVID pain intensity during the past 7 days on the scale from 0 to 10, where 0 is no pain and 10 is pain as bad as you can imagine:



Appendix 4: Post-COVID-19 Functional Status Scale (PCFS)

Patient questionnaire for patient self-report of the Post-COVID-19 Functional Status Scale

How much are you currently affected in your everyday life by COVID-19? **Please indicate which one of the following statements applies to you most.** *Please tick only one box at a time.*		**Corresponding PCFS scale grade if the box is ticked**
I have no limitations in my everyday life and no symptoms, pain, depression or anxiety.	☐	0
I have negligible limitations in my everyday life as I can perform all usual duties/activities, although I still have persistent symptoms, pain, depression or anxiety.	☐	1
I suffer from limitations in my everyday life as I occasionally need to avoid or reduce usual duties/activities or need to spread these over time due to symptoms, pain, depression or anxiety. I am, however, able to perform all activities without any assistance.	☐	2
I suffer from limitations in my everyday life as I am not able to perform all usual duties/activities due to symptoms, pain, depression or anxiety. I am, however, able to take care of myself without any assistance.	☐	3
I suffer from severe limitations in my everyday life: I am not able to take care of myself and therefore I am dependent on nursing care and/or assistance from another person due to symptoms, pain, depression or anxiety.	☐	4

Appendix 5: List of CYP3A4 Inhibitors

Taken from Table 3, FDA Draft Guidance for Industry: Drug Interaction Studies—Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations; Feb 2012; updated 26 Sept 2016). Excluded strong CYP3A4 inhibitors are listed in the far-left column of the table.

	Strong Inhibitors **≥ 5-fold increase in AUC** **Or, > 80% decrease in CL**	**Moderate Inhibitors** ≥ 2 but < 5-fold increase in AUC Or 50-80% decrease in CL	**Weak Inhibitors** ≥ 1.25 but < 2-fold increase in AUC Or, 20-50% decrease in CL
CYP3A4	**boceprevir**	amprenavir	alprazolam
	clarithromycin	aprepitant	amiodarone
	cobicistat	atazanavir	amlodipine
	conivaptan	cimetidine	atorvastatin
	danoprevir	ciprofloxacin	bicalutamide
	(darunavir)*	clotrimazole	chlorzoxazone
	(dasabuvir)*	crizotinib	cilostazol
	diltiazem	cyclosporine	fosaprepitant
	elvitegravir	dronedarone	fluoxetine
	grapefruit juice	erythromycin	gingko
	idelalisib	fluconazole	goldenseal
	indinavir	fluvoxamine	isoniazid
	itraconazole	fosamprenavir	istradefylline
	ketoconazole	imatinib	ivacaftor
	lopinavir	tofisopam	lapatinib
	mibefradil	verapamil	lomitapide
	nefazodone		nilotinib
	nelfinavir		oral contraceptives
	(ombitasvir)*		pazopanib
	paritaprevir		ranitidine
	posaconazole		ranolazine
	ritonavir		tacrolimus
	saquinavir		tipranavir/ritonavir
	telaprevir		ticagrelor
	telithromycin		zileuton
	tipranavir		
	troleandomycin		
	voriconazole		

Source: Table 3-2, https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm
* Ritonavir is usually given in combination with other anti-HIV or anti-HCV drugs in clinical practice. Caution should be used when extrapolating the observed effect of ritonavir alone to the effect of combination regimens on CYP3A activities.

Appendix 6: Sheehan Disability Scale

SHEEHAN DISABILITY SCALE

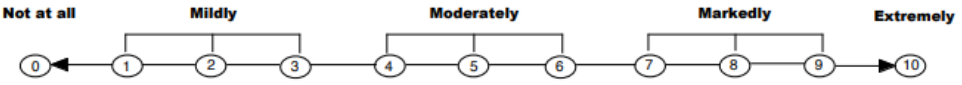
A BRIEF, PATIENT RATED, MEASURE OF DISABILITY AND IMPAIRMENT

Please mark ONE circle for each scale.

In the past week:

WORK* / SCHOOL

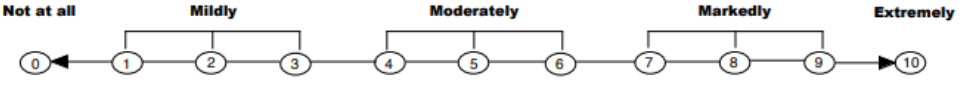
The symptoms have disrupted your work / school work:



☐ I have not worked /studied at all during the past week **for reasons unrelated to the disorder**.
* Work includes paid, unpaid volunteer work or training. If your symptoms interfered with your ability to find or hold a job or contributed in any way to your currently not working, you must give a score on this scale.

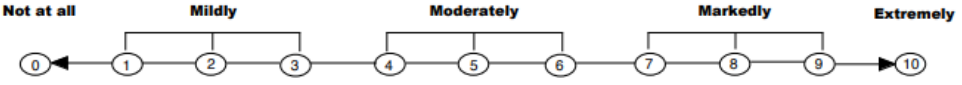
SOCIAL LIFE

The symptoms have disrupted your social life / leisure activities:



FAMILY LIFE / HOME RESPONSIBILITIES

The symptoms have disrupted your family life / home responsibilities:



DAYS LOST

On how many days in the past week did your symptoms cause you to miss school or work or leave you unable to carry out your normal daily responsibilities? _____

DAYS UNDERPRODUCTIVE

On how many days in the past week did you feel so impaired by your symptoms, that even though you went to school or work or had other daily responsibilities, your productivity was reduced? ____

Appendix 7: PROMIS – Sleep Disturbance Scale

PROMIS® Item Bank v1.0 – Sleep Disturbance – Short Form 8a

Sleep Disturbance – Short Form 8a

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Very poor	Poor	Fair	Good	Very good
Sleep109	My sleep quality was	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

	In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
Sleep116	My sleep was refreshing.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep20	I had a problem with my sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep44	I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep108	My sleep was restless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep72	I tried hard to get to sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep67	I worried about not being able to fall asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep115	I was satisfied with my sleep.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

English
16 March 2020

Page 1 of 1

Appendix 8: PROMIS – Fatigue Scale

PROMIS® Item Bank v1.0 – Fatigue – Short Form 8a

Fatigue – Short Form 8a

Please respond to each question or statement by marking one box per row.

	During the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
HI7	I feel fatigued.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3	I have trouble starting things because I am tired.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	In the past 7 days…					
FATEXP41	How run-down did you feel on average?..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40	How fatigued were you on average?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP35	How much were you bothered by your fatigue on average?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP49	To what degree did your fatigue interfere with your physical functioning?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	In the past 7 days…	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
FATIMP3	How often did you have to push yourself to get things done because of your fatigue?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP16	How often did you have trouble finishing things because of your fatigue?..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

English
16 March 2020

Page 1 of 1

Appendix 9: PROMIS – Cognitive Function - Abilities

PROMIS® Item Bank v2.0 – Cognitive Function – Abilities Subset—Short Form 8a

Cognitive Function - Abilities—Short Form 8a

Please respond to each question or statement by marking one box per row.

In the past 7 days...

		Not at all	A little bit	Somewhat	Quite a bit	Very much
PC43_2r	My mind has been as sharp as usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PC44_2r	My memory has been as good as usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PC45_2r	My thinking has been as fast as usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PC47_2r	I have been able to keep track of what I am doing, even if I am interrupted	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PC6r	I have been able to concentrate	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PC-CaPS3r	I have been able to think clearly without extra effort	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PC29_2r	I have been able to pay attention and keep track of what I am doing without extra effort	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PC-CaPS14r	I have been able to remember things as easily as usual without extra effort.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

02 January 2020
 Page 1 of 1

Appendix 10: Patient Global Impression of Change (PGI-C) Assessment

Patient's Global Impression of Change (PGIC) Scale

To be completed by the patient

Since the Start of the Study, Overall My Long COVID Symptoms (Specifically Pain, Sleep Disturbance, Fatigue, and/or Memory/Concentration Issues) Are:

Please Circle Your Answer

1 = Very Much Improved

2 = Much Improved

3 = Minimally Improved

4 = No Change

5 = Minimally Worse

6 = Much Worse

7 = Very Much Worse

Appendix 11: Insomnia Severity Index (ISI)

Insomnia Severity Index (ISI)

Subject ID: _____ **Date:** _____

For each question below, please circle the number corresponding most accurately to your sleep patterns in the **LAST MONTH.**

For the first three questions, please rate the **SEVERITY** of your sleep difficulties.

1. Difficulty falling asleep:

None	Mild	Moderate	Severe	Very Severe
0	1	2	3	4

2. Difficulty staying asleep:

None	Mild	Moderate	Severe	Very Severe
0	1	2	3	4

3. Problem waking up too early in the morning:

None	Mild	Moderate	Severe	Very Severe
0	1	2	3	4

4. How **SATISFIED/DISSATISFIED** are you with your current sleep pattern?

Very Satisfied	Satisfied	Neutral	Dissatisfied	Very Dissatisfied
0	1	2	3	4

5. To what extent do you consider your sleep problem to **INTERFERE** with your daily functioning (e.g., daytime fatigue, ability to function at work/daily chores, concentration, memory, mood).

Not at all Interfering	A Little Interfering	Somewhat Interfering	Much Interfering	Very Much Interfering
0	1	2	3	4

6. How **NOTICEABLE** to others do you think your sleeping problem is in terms of impairing the quality of your life?

Not at all Noticeable	A little Noticeable	Somewhat Noticeable	Much Noticeable	Very Much Noticeable
0	1	2	3	4

7. How **WORRIED/DISTRESSED** are you about your current sleep problem?

Not at all	A Little	Somewhat	Much	Very Much
0	1	2	3	4

USA-Canada/English (original)
ISI_AU2.1-last-month_eng-CA-USori

Appendix 12: Epworth Sleepiness Scale (ESS)

Epworth Sleepiness Scale

Subject ID: _____ Today's date: _____

Your age (yrs): _____ Your sex (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired?

This refers to your usual way of life recently.

Even if you haven't done some of these things recently, try to figure out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = **no chance** of dozing
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each item as best as you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading	___
Watching TV	___
Sitting inactive in a public place (e.g., a theater or a meeting)	___
As a passenger in a car for an hour without a break	___
Lying down to rest in the afternoon when circumstances permit	___
Sitting and talking to someone	___
Sitting quietly after a lunch without alcohol	___
In a car, while stopped for a few minutes in traffic	___

THANK YOU FOR YOUR COOPERATION

ESS - United States/English - Version of 01 Feb 2021 - Mapi.
ID037309 / ESS_AU1.0_eng-US2.doc

Appendix 13: eDiary

- The eDiary will include Login, Welcome, Content (eDiary Questions), and Entry Confirmation/Submission pages
- **Content (eDiary Questions)**
  - Question #1: Worst Long COVID Pain (24-hour recall)
    - Rate your worst Long COVID pain intensity during the last 24 hours on a scale from 0-10, where 0 is NO PAIN and 10 is PAIN AS BAD AS YOU CAN IMAGINE.
      - Patient selects a response by moving the 0-10 point slider to the appropriate whole number score
  - Question #2: Sleep Quality (24-hour recall)
    - Rate your sleep quality last night on a scale from 0-10, where 0 is the BEST POSSIBLE SLEEP and 10 is the WORST POSSIBLE SLEEP
      - Patient selects a response by moving the 0-10 point slider to the appropriate whole number score
  - Question #3 (Post-Randomization): Study Drug
    - Did you take your study drug last night?
      - Patient selects yes or no
  - Question #4 (Post-Randomization): Study Drug
    - How many tablets of study drug did you take last night?
      - Patient selects 0, 1, or 2
- **Entry Confirmation/Submission**
  - A summary page is displayed showing the patient's entries for each question
  - Please confirm your answers below
    - Pain: __
    - Sleep: ___
    - Medication Taken: ___
    - Tablets Taken: ___
  - If all entries are correct the patient will press submit.
  - If the patient needs to revise their entries, they can press the back button to re-do.