TNX-CY-F304

A PHASE 3, DOUBLE-BLIND, RANDOMIZED, MULTICENTER, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF TNX-102 SL TAKEN DAILY AT BEDTIME IN PATIENTS WITH FIBROMYALGIA
"RELIEF STUDY"

Document Date: 27 MARCH 2020

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Tonix Pharmaceuticals, Inc. • 26 Main Street, Suite 101 Chatham, NJ 07928 • Tel: 862.904.8182

TONIX PHARMACEUTICALS

TNX-102 SL (CYCLOBENZAPRINE HCL SUBLINGUAL TABLETS)

TNX-CY-F304
A PHASE 3, DOUBLE-BLIND, RANDOMIZED, MULTICENTER, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF TNX-102 SL TAKEN DAILY AT BEDTIME IN PATIENTS WITH FIBROMYALGIA
"RELIEF STUDY"

Original Protocol Release Date: 03 JULY 2019
Amendment 01: 18 OCTOBER 2019
Amendment 02: 27 MARCH 2020
US IND No. 112512

Sponsor:
Tonix Pharmaceuticals, Inc. (Tonix)
509 Madison Avenue, Suite 1608
New York, NY 10022

For Tonix:

[redacted]

INVESTIGATOR'S AGREEMENT

I have read the TNX-CY-F304 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.

_____
Printed Name of Investigator

_____
Signature of Investigator

_____
Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Responsible Sponsor Physician	[redacted]	[redacted]
24-Hour emergency contact	[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 3, Double-Blind, Randomized, Multicenter, Placebo-Controlled Study to Evaluate the Efficacy and Safety of TNX-102 SL Taken Daily at Bedtime in Patients with Fibromyalgia (Protocol No. TNX-CY-F304)

Study center(s): 35 to 45 centers in the United States (US)

Estimated Studied period: 14 months Estimated date first patient enrolled: Nov 2019 Estimated date last patient completed: Dec 2020	**Phase of development: 3**

Objectives:

Primary
To evaluate the efficacy of TNX-102 SL (cyclobenzaprine HCl sublingual tablets) 5.6 mg in the treatment of patients with fibromyalgia.

Secondary
To evaluate the safety of TNX-102 SL (cyclobenzaprine HCl sublingual tablets) 5.6 mg in the treatment of patients with fibromyalgia.

Methodology:
This is a Phase 3, 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 daily at bedtime for the treatment of fibromyalgia. The study is to be conducted at approximately 35-45 investigational sites in the United States.

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. For extenuating circumstances, the duration of the Screening period may be increased to up to 49 days with Medical Monitor approval. Note, this trial was ongoing at the time the SARS-CoV-2 virus began to spread in the US, leading to the illness known as COVID-19 that is part of the COVID-19 pandemic. 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 (Visit 3, 4, 5), and, only with Medical Monitor approval, Week 14/Visit 6 (or Early Termination) for those unable to attend an in-clinic visit due to the COVID-19 pandemic. 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 Early Termination), a home visit should be conducted rather than a telephone

visit in order to collect greater safety data than the telephone visits allow. The Screening phase will be followed by the Baseline/Randomization Visit (Visit 2, Day 1), and 4 treatment visits at Weeks 2, 6, 10, and 14 (or Early Termination). The total duration of the study, including Screening, will be approximately 15-19 weeks. The maximum treatment duration will be 14 weeks.

Eligible patients who provide written informed consent will have study assessments performed at Screening and will stop all excluded medications during the washout period through the Week 14 visit (Visit 6). Patients will record their average pain intensity for the previous 24 hours in the evening every day from Visit 1 through Visit 6 on a diary system. After recording Baseline Diary scores for at least 7 days, patients will return to the investigative site for Baseline assessments and randomization (Day 1), where they will be randomly assigned to receive TNX-102 SL or matching placebo sublingual tablets in a 1:1 ratio.

Patients will take the study drug sublingually daily at bedtime, starting on the day that they are randomized (Day 1), for 14 weeks. For the first two weeks of treatment, patients will start on TNX-102 SL 2.8 mg (1 tablet) or placebo. Upon return to the site[1] for the Week 2 visit (Visit 3), all patients will have the dose increased to TNX-102 SL 5.6 mg (2 x 2.8 mg tablets) or two placebo tablets. Patients will return to the site[1] for assessment of efficacy and safety, as well as dose tolerability, at Weeks 6, 10, and 14 (or Early Termination).

In scenarios in which TNX-102 SL 5.6 mg, or 2 placebo tablets, is considered intolerable and would otherwise lead to study discontinuation, the Investigator may lower the dose back to 1 tablet every night (TNX-102 SL 2.8 mg or one placebo tablet). Re-challenge with 2 tablets TNX-102 SL 2.8 mg (5.6 mg dose)/placebo may be attempted at a later date if/when it is deemed clinically warranted by the Investigator, or the patient may remain on the lower dose for the remainder of the study.

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

Patients will be trained on use of the diary system at the Screening visit. Each evening, when the patient utilizes the diary, the system will prompt the patient regarding daily average pain intensity, sleep quality from the previous night, and study drug dosing the previous night (post-randomization).

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 medication-free for at least 21 days prior to randomization. This will provide 14 days off the excluded medication before the patient starts the 7-day run-in phase during which critical baseline daily diary efficacy data are collected. Any additional time required for down-titration would be in addition to this 21-day washout requirement. For this reason, patients can remain in screening for up to 35 days, which provides an additional 2 weeks for down-titration, if required.

Number of patients (planned):
Approximately 470 patients 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.

[1] All references to a site/study center visit for Weeks 2, 6, 10, and 14 include telephone visits for Weeks 2, 6, and 10, and home visits or telephone visit for Week 14/ET that are being allowed due to the circumstances of the COVID-19 pandemic.

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 diagnosis of primary FM as defined by the 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria (American College of Rheumatology Preliminary Diagnostic Criteria), which includes all of the following:
   a. Generalized pain, defined as pain in at least 4 of 5 regions
   b. Symptoms have been present at a similar level for at least 3 months; and
   c. Widespread pain index (WPI) ≥7 and symptom severity scale (SSS) score ≥5; OR WPI between 4-6 and SSS scale score ≥9; and
   d. The patient does not have another disorder that would otherwise explain his/her pain.
3. The in-clinic 7-day recall NRS average daily pain intensity score at Screening Visit must be ≥ 4 and ≤ 9. Exceptions are only possible with Medical Monitor approval.
4. If female, is either not of childbearing potential (defined as postmenopausal for at least 1 year or surgically sterile [e.g., bilateral tubal ligation, bilateral oophorectomy, or hysterectomy]) or will be practicing one of the following methods of birth control throughout the study:
   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 (IUD);
   c. Double-barrier method (condoms, sponge, diaphragm, or vaginal ring with spermicidal jelly or cream);
   d. Partners of vasectomized males in stable relationships;
   e. Females involved in stable same sex relationships;
   f. Female patients practicing abstinence may have the birth control requirement waived only with Medical Monitor approval.
5. Patients currently receiving non-exclusionary pharmacologic treatment for depression should have been clinically stable for at least 3 months prior to randomization, and on stable doses of the antidepressant regimen during this 3-month time frame.
6. 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 formulations of cyclobenzaprine, and benzodiazepines.
7. The patient is willing and able to comply with all protocol-specified requirements.
8. The patient is capable of reading and understanding English and has provided written informed consent to participate. Separate written, signed informed consent will be required if the patient is to participate in the optional pharmacogenomic assessment. A decision not to participate in optional pharmacogenomic testing will not affect the patient's eligibility for the main study.
9. In addition to satisfying all other eligibility and randomization criteria, the patient has also received Medical Monitor Pre-Randomization Approval to proceed to the Baseline/Randomization visit.

Exclusion criteria (Assessed at Screening Visit 1):

1. The patient has been diagnosed with infectious or inflammatory arthritis (e.g., rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis), systemic lupus erythematosus, untreated or active gout (ie, any acute attacks within past 2 years is exclusionary), or meets criteria for other type of systemic autoimmune disease.

2. The patient has been diagnosed with a complex regional pain syndrome, failed back surgery syndrome, persistent or prevalent pain symptoms related to systemic disease (e.g., diabetic peripheral neuropathy, post-herpetic neuropathy), untreated hyperparathyroidism, or a history of prior surgery, trauma or other source of pain that, in the Investigator's opinion, would confound or interfere with the assessment of the patient's fibromyalgia pain 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), and Module K (Psychotic 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). Any patient who scores ≥ 7 on the MSI-BPD may be randomized only with Medical Monitor approval.
5. The patient is at increased risk of suicide on the basis of the Investigator's judgment, or the results of the Beck Depression Inventory-II (BDI-II) (a response > 1 to BDI-II item #9), or the results of the Columbia Suicide Severity Rating Scale (C-SSRS) conducted at Screening and Baseline (e.g., C-SSRS Type 3, 4 or 5 ideation during the preceding 6 months and any suicidal behavior within the past 12 months).
6. A BDI-II score greater than 24 at either the Screening or Baseline visit.
7. The patient has participated in any other study with TNX-102 SL.
8. Based on screening laboratory results, TSH > 1.5 times the upper limit of normal or AST or ALT > 2 times the upper limit of normal; 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 (e.g., significant arrhythmia; heart block; heart failure; symptomatic coronary artery disease), 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 has a known current clinically significant systemic infection (e.g., HIV, hepatitis).
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 EC#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 wash-out of the following medications during screening, or wash-out is inadvisable: monoamine oxidase inhibitors (30 day washout required), levomilnacipran, anticonvulsants (except when used for migraine prophylaxis), amphetamine mixed salts, weight loss agents such as phentermine and diethylpropion, muscle relaxants (e.g., methocarbamol, baclofen, carisoprodol), stimulants (e.g., methylphenidate, lisdexamfetamine, dextroamphetamine), mirtazapine, trazodone, nefazodone, St. John's wort, any medication known to be a strong CYP3A4 inhibitor (Appendix 1), or any of the medications listed in Inclusion Criterion #6.
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, or interfere with 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 known hypersensitivity to cyclobenzaprine or the excipients in TNX-102 SL or placebo formulations.
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 (e.g., apnea/hypopnea index 5-15), and/or patients whose mild to moderate sleep apnea is well-controlled with CPAP or oral device, are allowed at the discretion of the Investigator. Due to the increased risk of sleep apnea, any patient with a BMI >45 must receive Medical Monitor approval prior to randomization.
25. The patient has a history of narcolepsy, cataplexy, periodic involuntary limb movement disorder or other documented, clinically significant sleep disorder.
26. Patient has plans for international travel, or has a work schedule (e.g., requiring night shifts), that prevents them from being able to utilize the diary system during its available time window or to take study drug on a regular basis.
27. The patient is currently being treated with sodium oxybate or ketamine or CGRP receptor antagonists.
28. The patient is currently filing or seeking a work disability claim for any reason or condition.
29. The patient has received an investigational calcitonin gene-related peptide (CGRP) receptor antagonist within 90 days of Screening, or any other investigational drug within 30 days of Screening.

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 FM pain satisfies the following criteria, as assessed by diary pain scores (24-hour recall):
    - 2a. A mean pain intensity score ≥4 and ≤9 on the 11-point (0-10) NRS scale for the 7 days immediately preceding Visit 2, and
    - 2b. No more than 2 individual days with a score <4 on the 7 days immediately preceding Visit 2, and
    - 2c. No score of 10 on any of the 7 days immediately preceding Visit 2, and
    - 2d. 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 starting on Day 1 for 2 weeks; then patient will take 2 tablets of assigned study drug simultaneously and sublingually starting on Day 15 for 12 weeks. If necessary, 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 dose of 2 tablets (5.6 mg) is considered intolerable and would otherwise lead to study discontinuation, the Investigator may lower the dose back to 1 tablet (2.8 mg) per day. Re-challenge with 2 tablets (5.6 mg) may be attempted at a later date if/when deemed clinically warranted.

Criteria for Evaluation:

Efficacy:

Primary efficacy endpoint:

- Change from Baseline to the Week 14 endpoint in the diary NRS weekly average of daily self-reported average pain severity scores.

Secondary efficacy endpoints: The 6 secondary efficacy endpoints listed below are considered key secondary endpoints and will be tested in that order:

- Proportion of patients with a Patient's Global Impression of Change (PGIC) rating of "very much improved" or "much improved" at the Week 14 endpoint
- Change from baseline in the Fibromyalgia Impact Questionnaire – Revised (FIQR) symptoms domain score at the Week 14 endpoint
- Change from baseline in the FIQR function domain score at the Week 14 endpoint
- Change from baseline in the Patient Reported Outcomes Measurement Information System (PROMIS) score for sleep disturbance at the Week 14 endpoint
- Change from baseline in the PROMIS score for fatigue at the Week 14 endpoint
- Change from baseline in the weekly average of the daily diary assessment of sleep quality at the Week 14 endpoint

Exploratory efficacy endpoints:

- Proportion of patients with a ≥30% improvement from baseline to Weeks 1-14 in the daily self-reported average pain severity score
- Proportion of patients with a ≥50% improvement from baseline to Weeks 1-14 in the daily self-reported average pain severity scores
- Proportion of patients with a PGIC rating of "very much improved" or "much improved" at all post-randomization clinic visits
- Change from baseline in the FIQR total score, overall impact domain score, and individual item scores at all post-randomization clinic visits
- Change from baseline in the FIQR symptoms domain score and function domain scores at all post-randomization clinic visits
- Change from baseline in the PROMIS score for sleep disturbance at all post-randomization clinic visits
- Change from baseline in the PROMIS score for fatigue at all 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 self-reported average pain severity scores at Weeks 1-14
- Changes from baseline in patient-rated Changes in Sexual Functioning Questionnaire Short-Form (CSFQ-14) in females and in males, analyzed separately

Safety:

- Incidence of adverse events
- 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 the C-SSRS scale
- Changes from baseline in BDI-II scores

Concomitant Medications:

Patients who are taking certain medications to manage their FM 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 milnacipran, pregabalin, duloxetine, tramadol, tapentadol, gabapentin and other anticonvulsants (aside from those used as migraine prophylaxis), any form of cyclobenzaprine (AMRIX®, or generic equivalents), amitriptyline and other tricyclic antidepressants, trazodone, narcotics/opioids, naltrexone (including CONTRAVE®) and benzodiazepines.

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 for at least 30 days at a stable dose (except for allowed antidepressants, which require 90 days at stable dose) prior to the date of randomization, and usage is expected to remain stable throughout 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 (e.g., trazodone, mirtazapine, levomilnacipran, nefazodone, benzodiazepines, non-benzodiazepine sleep aids, stimulants, sodium oxybate, ketamine, 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 (e.g. 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 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 adverse events. If there is a requirement for acute opioids, corticosteroids, or other treatments that could confound the evaluation of pain at critical times (defined as the week prior to Clinic Visits 2, 3, 4, 5 or 6), 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 clinic visit.

Statistical methods:

Efficacy Analyses:

The primary efficacy parameter will be the contrast between TNX-102 SL and placebo in the weekly mean change from baseline pain score at the endpoint visit. The weekly pain score will be based on the weekly average of the daily diary patient self-reported 24-hour recall average pain severity scores using an 11-point (0-10) NRS.

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 average pain severity 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 for missing data. Covariates in the model will include the fixed categorical effects of treatment, center, 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.

Safety Analyses:

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized overall and by preferred term and system organ class. Adverse events 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, SD, median, 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. [redacted]

Pharmacogenomic Analyses
Potential genetic determinants of treatment response will be examined by the assessment of genetic variants in relation to treatment outcome. A blood sample will be obtained from patients who have signed a separate informed consent form for the pharmacogenomic analyses. The blood sample can be obtained at any visit post Screening, and the patient has agreed to be tested and has signed the separate informed consent form; i.e., the blood draw is not tied to any specific study visit, hence it can be obtained at any time post Screening. But due to circumstances caused by the COVID-19 pandemic and 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).
The first step of the pharmacogenomic analyses will involve exome sequencing and analysis for allelic polymorphisms related to treatment response to TNX-102 SL. It is presumed that unused sample will be stored up to fifteen 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]	Run-In Period (Diary for Symptoms)	Baseline/ Random-ization	Week 2 [r]	Week 6 [r]	Week 10 [r]	Week 14/ET[b]
Study Day	**Day -35 to -1**	**Day -7 to -1**	**Day 1**	**Day 15 -4 /+7 days**	**Day 43 ± 7 days**	**Day 71 ± 7 days**	**Day 99 -4 /+7 days**
Visit Number	**1**		**2**	**3**	**4**	**5**	**6**
Informed consent	X						
Inclusion/exclusion criteria	X						
Demographics	X						
Medical history	X		X[k]				
Prior/Concomitant medications	X		X[k]	X	X	X	X
Lifetime FM pharmacotherapy history	X						
Physical examination	X		X[c]				X
Inspection of oral cavity[n]	X		X	X	X	X	X
2016 Revision to 2010/2011 FM Diagnostic Criteria	X						
MINI 7.0.2 Modules A, C, I, J, K (MDE, Bipolar, EtOH, Substance Use, Psychotic Disorders)	X						
MSI-BPD	X						
Columbia-Suicide Severity Rating Scale (C-SSRS)	X		X	X	X	X	X
Beck Depression Inventory (BDI-II) [q]	X		X	X	X	X	X
In-clinic assessment of pain (24-hour & weekly recall) [q]	X[p]		X	X	X	X	X
FIQR [q]			X	X	X	X	X
PROMIS – Sleep Disturbance [q]			X	X	X	X	X
PROMIS - Fatigue [q]			X	X	X	X	X
PGIC Assessment [q]				X	X	X	X
CSFQ-14 (female or male version, as appropriate) [q]			X				X

Assessment	Screening and Washout Period[a]	Run-In Period (Diary for Symptoms)	Baseline/ Random-ization	Week 2 [r]	Week 6 [r]	Week 10 [r]	Week 14/ET[b]
Study Day	**Day -35 to -1**	**Day -7 to -1**	**Day 1**	**Day 15 -4 /+7 days**	**Day 43 ± 7 days**	**Day 71 ± 7 days**	**Day 99 -4 /+7 days**
Visit Number	**1**		**2**	**3**	**4**	**5**	**6**
Clinical laboratory tests[d]	X, X[a]						X
Drug screen	X[m]						
Pregnancy test[e]	X		X	X	X	X	X
Vital signs[f]	X		X	X	X	X	X
12-lead electrocardiogram[g]	X						
Randomization criteria and procedures			X				
Patient training and diary review[h]	X		X	X	X	X	X
Diary assessment of 24-hour recall of pain (daily)[j]	X	X	X	X	X	X	X
Dispense double-blind study drug[i]			X	X	X	X	
Study drug compliance				X	X	X	X
Dose Tolerability Assessment				X	X	X	X
Pharmacogenomic blood draw (optional)[o]			*	*	*	*	*
Adverse events			X	X	X	X	X
Assess diary compliance			X	X	X	X	X

Abbreviations: ACR=American College of Rheumatology; BDI-II = Beck Depression Inventory-II; BPD= Borderline personality disorder; CSFQ-14 = Changes in Sexual Functioning Questionnaire Short-Form; C-SSRS = Columbia-Suicide Severity Rating Scales; ET = Early Termination; FIQR = Fibromyalgia Impact Questionnaire-Revised; FM=Fibromyalgia; MINI= Mini International Neuropsychiatric Interview; MSI-BSP McLean Screening Instrument for BPD;=PGIC = Patient Global Impression of Change; PROMIS = Patient Reported Outcomes Measurement Information System;;

[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 that 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 need to 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. All benzodiazepine drug screening must be sent to the central laboratory for analysis and confirmed negative prior to randomization,

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

[d] Clinical laboratory tests (hematology and serum biochemistry) will be performed at Screening and Week 14/ET. For patients where a telephone visit is being conducted for Week 14/ET, the laboratory tests will not be required. TSH will be tested at Screening only. Optional HCV/HBsAg testing may be performed at Screening at the discretion of the Investigator or Sponsor. Medical Monitor approval is required prior to testing.

[e] 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 where a telephone visit is being conducted, the urine pregnancy test will be performed at home by patient for women of child-bearing potential.

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

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

[h] Clinic staff members will train the patient on how to take the study drug and how to complete the diary. Patients will be asked to complete their diary every evening. Diary completion will start on the evening of Visit 1 and continue through Week 14. Diary responses will be monitored during the study.

[i] 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 where a telephone visit is being conducted, the study drug will be mailed via courier to their home. Patients will be instructed to take one 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.

[j] Patients will assess their average daily 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.

[k] Any additional (pre-screening) medical findings or medications discovered after the Screening Visit are to be noted in the Medical History, Prior/Concomitant Medication Page or Lifetime FM pharmacotherapy page, respectively.

[l] PROMIS scales for sleep disturbance and fatigue.

[m] The urine drug screen is mandatory at Visit 1. If the screening 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 V2. 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] 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 in which a visual exam is not possible (i.e. 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.

*/[o] The blood draw for the pharmacogenomic assessment can be obtained at any study visit post-Screening (including an Early Termination visit). Due to circumstances caused by the COVID-19 pandemic and 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.

[p] Weekly recall of daily average pain intensity on the NRS scale is required at the Screening Visit. Patients should only continue screening if they score ≥4 and ≤9. A score outside this range will require Medical Monitor approval in order to continue in screening.

[q] For telephone visits, the patient will be mailed all the applicable patient reported outcomes for a given visit. The results of the BDI-II will be reviewed with the patient (specifically Question #9 which will allow further exploration of any suicidal thoughts or wishes implied by the patient's self-reported response, if applicable) during the phone call. C-SSRS interview should only be conducted after the BDI-II Question #9 inquiry, as any discrepancy between Question #9 response and C-SSRS suicidal ideation types endorsed for the same assessment period must be resolved to avoid presence of occult suicidal ideation not recognized by site staff.

[r] Week 2, Week 6, and the 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 (e.g. 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 (e.g. 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.

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

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LIST OF TABLES

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
BDI-II	Beck Depression Inventory-II
BPD	borderline personality disorder
BUN	blood urea nitrogen
CBD	cannabidiol
CBP	cyclobenzaprine HCl
CFR	Code of Federal Regulations
CGRP	calcitonin gene-related peptide
CHW	Cui, Hung, Wang
CI	confidence interval
CK	creatine kinase
COVID-19	Coronavirus Disease 2019 - viral illness caused by SARS-CoV-2
CPAP	continuous positive airway pressure
CRF	case report form
CRO	contract research organization
CSFQ-14	Changes in Sexual Functioning Questionnaire Short-Form
C-SSRS	Columbia- Suicide Severity Rating Scale
CYP3A4	cytochrome P450 subtype 3A4
e.g.	*exempli gratia* (for example)
EC	ethics committee
ECG	electrocardiogram
ER	extended release
ET	early termination, i.e. discontinuation from trial
EULAR	European League of Against Rheumatism
PROs	Patient-Reported Outcome assessments
etc.	*et cetera* (and other things)
FDA	US Food and Drug Administration
FM	fibromyalgia
FIQR	Fibromyalgia Impact Questionnaire (Revised)
g	gram(s)
GCP	good clinical practice
GLP	good laboratory practice
H, h	hour(s)
HCl	hydrochloride
HIPAA	Health Insurance Portability and Accountability Act
HIV_1	human immunodeficiency virus type 1

HIV_2	human immunodeficiency virus type 2
i.e.	*id est* (that is)
ICF	informed consent form
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IR	immediate release
IRB	institutional review board
IRT	Interactive Response Technology
ITT	intent-to-treat
IUD	intrauterine device
kg	kilogram(s)
L	liter(s)
LBBB	left bundle branch block
LS	least squares
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA®	*Medical Dictionary for Regulatory Activities*®
mg	milligram(s)
min	minute(s)
MINI	Mini International Neuropsychiatric Interview
mL	milliliter(s)
mmHg	millimeter(s) of mercury
MMRM	mixed-effects model repeated-measures
msec	millisecond(s)
MSI-BPD	McLean Screening Instrument for BPD
N, n	number (of patients)
NA	no activity
NA	not applicable
nCBP	norcyclobenzaprine
NDA	New Drug Application
ng	nanogram(s)
nM	nanomolar(s)
NRS	Numeric Rating Scale
NSAID	nonsteroidal anti-inflammatory drug
PGIC	Patient Global Impression of Change
pH	approximate negative logarithm of the hydrogen ion concentration
PO	*per os* (by mouth)
PRN	*pro re nata* (as needed)
PRO	patient-reported outcome
PROMIS	Patient Reported Outcomes Measurement Information System
PTSD	posttraumatic stress disorder
QTcF	QT corrected for heart rate using Fridericia's formula
RBC	red blood cell
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
SD	standard deviation
SE	standard error
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SL	sublingual
SNRI	serotonin-norepinephrine reuptake inhibitor
SOC	system organ class
SOP	standard operating procedure
SSS	symptom severity scale
SSRI	selective serotonin reuptake inhibitor
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
vs.	versus
WBC	white blood cell
WHO	World Health Organization
WPI	Widespread Pain Index

5. INTRODUCTION

5.1. Overview of Fibromyalgia

Fibromyalgia (FM) is a musculoskeletal pain disorder of unknown etiology. The prevalence of FM in the United States (US) is estimated at 2%; occurring in approximately 3.4% of females and 0.5% of males (Wolfe, et al. 1995). In addition to diffuse myalgia, FM is characterized by chronic fatigue, psychological distress, and disturbed and unrefreshing sleep (Wolfe, et al. 2010; Wolfe, et al. 1995; Campbell, et al. 1982; Smythe, et al. 1985). Potential triggers of FM include psychological factors (Payne, et al. 1982; Ahles, et al. 1984; Wolfe, et al. 1984), mechanical stresses in the cervical and lumbar spine (Lewis, et al. 1939), muscle deconditioning (Bennett, et al. 1989), neurotransmitter abnormalities (Russell 1989), and disturbances in the chronobiology of sleep-wakefulness (Moldofsky 1994).

5.2. Background of TNX-102 SL

TNX-102 SL (cyclobenzaprine HCl sublingual tablets) is being developed as 505(b)(2) NDAs for FM, posttraumatic stress disorder (PTSD), and Agitation in Alzheimer's Disease using AMRIX (extended-release capsule [ER], 30 mg; AMRIX® Prescribing Information, May 2018) as the reference listed drug. The TNX-102 SL is a formulation containing 2.8 mg cyclobenzaprine HCl [3-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-N,N-dimethyl-1-propanamine hydrochloride] for 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 TID or 5 mg TID, respectively. The FLEXERIL brand of immediate-release (IR) cyclobenzaprine tablets has been discontinued since May 2013. Generic cyclobenzaprine is available and marketed in a variety of strengths including 5-, 7.5- and 10-mg IR tablets. AMRIX® (AMRIX® Prescribing Information, 2018), an ER capsule of cyclobenzaprine was approved in 2007 in the US as a New Drug Applications (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 cyclobenzaprine product has been approved for use in FM by 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-HT_{2A}, α_1-adrenergic, H_1-histaminergic, and M_1-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.

[redacted]

5.3. Scientific Rationale

5.3.1. Use of CBP in the Management of FM

No CBP product has been approved for use in FM by FDA or in any other countries. Although CBP has been investigated for the treatment of FM, typically in a dosage range of tens of milligrams per day (Bennett, et al. 1988; Quimby, et al. 1989; Reynolds, et al. 1991; Santandrea, et al. 1993; Carette, et al. 1994; Fossaluzza et al. 1992), results of these studies have been equivocal. Side-effects typically associated with the use of CBP in this higher dosage range, including drowsiness, dry mouth, and dizziness, may have competed with a treatment effect.

Despite these equivocal results and significant side-effects in this higher dosage range, CBP is widely prescribed off-label as a treatment for FM. In part, the use of CBP has been encouraged by published FM treatment guidelines (Burckhardt, et al. 2005; Goldenberg, et al. 2004; Hauser, et al. 2010) including the recent European League of Associations for Rheumatology (EULAR) Revised Recommendations for the Management of Fibromyalgia, in which it was among the six recommended pharmacotherapies for FM (Macfarlane et al, 2017). An IMS Health prescription utilization study covering the period from January 1, 2007, to December 21, 2010, found that approximately 21% of patients diagnosed with fibromyalgia filled a prescription for CBP, and 41% of those patients used the drug for more than 90 days.

5.3.2. Rationale for Investigating Sublingual Dosing with CBP for Bedtime Administration to Treat Fibromyalgia

[redacted]

5.3.3. Brief Summary of Prior Clinical Experience and Dose Rationale

TNX-102 SL 2.8 mg tablet is a very low, sublingual dose of cyclobenzaprine hydrochloride; this dose was originally selected to minimize adverse events and improve tolerability in this especially medication-sensitive population (FDA 'The Voice of the Patients' Fibromyalgia Report, October 2014). [redacted]

[redacted]

5.4. Conclusion for Study Design

[redacted]

The present study is a Phase 3, randomized, double-blind, multicenter trial 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 compared to placebo over 14 weeks in patients with fibromyalgia. Since fibromyalgia patients are often quite sensitive to medication side effects, the protocol includes a 2 week dose titration starting at 2.8 mg dose, followed by an increase to 5.6 mg from Day 15 through end of study. Additionally, to mitigate the potential for discontinuations due to tolerability at 5.6 mg in the FM population, the protocol includes a provision for the Investigator to reduce the dose back to one tablet daily at bedtime, either temporarily, or for the duration of the study, in order to prevent missing data due to AE-related discontinuations. Even so, the goal and design of the study is to always encourage the continued dosing with TNX-102 SL 5.6 mg nightly after the initial 2-week dose titration phase, and it is anticipated that dose lowering will only rarely be necessary in the study.

6. TRIAL OBJECTIVES

6.1. Primary Objective

To evaluate the efficacy of TNX-102 SL (cyclobenzaprine HCl sublingual tablets) 5.6 mg in the treatment of patients with fibromyalgia.

6.2. Secondary Objective

To evaluate the safety of TNX-102 SL (cyclobenzaprine HCl sublingual tablets) 5.6 mg in the treatment of patients with fibromyalgia.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a Phase 3, double-blind, randomized, multicenter, 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 daily at bedtime for the treatment of fibromyalgia. The study is to be conducted at approximately 35-45 investigational sites in the United States.

The study will consist of a Screening Visit (Visit 1, Days -35 to -8), a Baseline/Randomization Visit (Visit 2, Day 1), a Week 2 Visit (where the dose will be increased to 5.6 mg/day), and 3 more treatment visits (Weeks 6, 10 and 14 or Early Termination). The period between the Screening and Baseline Visit wills be at least 7 days, in order to allow for at least one week of daily pain data collection, and up to 35 days, to accommodate any necessary scheduling challenges or prohibited medication washout time. For extenuating circumstances, the duration of the Screening period may be increased to up to 49 days with Medical Monitor approval, and an option for a telephone visit will be available for Weeks 2, 6, and 10 for those unable to attend an in-clinic visit due to circumstances related to the COVID-19 pandemic. Additionally, a Week 14/ET telephone visit or home visit by site staff may be allowed on a case-by-case basis, approved by the Medical Monitor, if the only other choice is losing the patient completely from the study if patient absolutely cannot come in to the clinic for the visit. The total duration of the study, including Screening, will be approximately 15-19 weeks. The maximum treatment duration will be 14 weeks.

Eligible patients who provide written consent will have study assessments performed at Screening and will stop all excluded medications during the washout period, as required, through the Week 14 visit (Visit 6). An in-clinic 7-day recall NRS average daily pain intensity score at Screening must be ≥ 4 and ≤ 9 in order for the patient to remain eligible. A score outside this range will require Medical Monitor approval to remain in screening.

Patients will be trained on the use of the daily diary at Screening Visit 1. Patients will be asked to record their average daily pain intensity on the 11-point (0-10) NRS scale using 24-hour recall, and to provide an assessment of sleep quality from the previous evening, also using an 11-point NRS scale. Each evening, when the patient completes the diary, the system will prompt the patient regarding daily average pain intensity, sleep quality from the previous night, and study drug dosing (post-randomization). Due to limitations in the diary completion window, patients that 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.

After completing any required washout of excluded therapies (see next paragraph) 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), where they will be randomly assigned to receive TNX-102 SL 5.6 mg (2 x 2.8 mg tablets) or matching placebo sublingual tablets in a 1:1 ratio. The mean of the 7 days immediately preceding Visit 2 (Baseline Randomization Visit; Day 1) will serve as the baseline pre-treatment pain score.

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 withdrawal must be accomplished so that the patient is medication-free for at least 21 days prior to randomization. This will provide 14 days off the excluded medication before the patient starts the 7-day run-in phase during which critical baseline efficacy data are collected by means of the daily diary. Any additional time required for gradual dose reduction/down-titration would be in addition to this 21-day washout requirement. For this reason, patients can remain in screening for up to 35 days, which provides an additional 2 weeks for down-titration, if required.

Patients will take the study drug sublingually daily at bedtime, starting in the evening of the day that they are randomized (Day 1, Visit 2), for 14 weeks. Patients will be instructed to take one tablet (2.8 mg) sublingually daily at bedtime for the first 2 weeks (Days 1-14). Patients will then return to the clinic[1] at Week 2 (Visit 3) for efficacy and safety assessments, assessment of study drug compliance, and the study drug dose will be increased to two tablets (2 x 2.8 mg) taken sublingually and simultaneously daily at bedtime. Patients will next return to the clinic[1] at Week 6 (Visit 4) for efficacy and safety assessments, assessment of study drug compliance, and an assessment of dose tolerability at the 5.6 mg dose. If the patient reports intolerable side effects at this visit (Visit 4), the Investigator may consider a reduction in dose to one tablet sublingually every night, either temporarily or for the remainder of the study, depending on what the Investigator considers clinically appropriate. 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 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 study center[1] for safety and efficacy assessments, and assessments of study drug compliance and tolerability at Weeks 10 (Visit 5), and 14 (Visit 6) or Early Termination.

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

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

7.2. Study Endpoints

7.2.1. Primary efficacy endpoint

Change from Baseline to the Week 14 endpoint in the diary NRS weekly average of daily self-reported average pain severity score.

[1] All references to a site/study center visit for Weeks 2, 6, 10, and 14 include telephone visits for Weeks 2, 6, and 10, and home visits or telephone visit for Week 14/ET that are being allowed due to the circumstances of the COVID-19 pandemic.

7.2.2. Secondary efficacy endpoints:

The 6 secondary efficacy endpoints listed below are considered key secondary endpoints and will be tested in that order.

- Proportion of patients with a Patient's Global Impression of Change (PGIC) rating of "very much improved" or "much improved" at the Week 14 endpoint
- Change from baseline in the Fibromyalgia Impact Questionnaire – Revised (FIQR) symptoms domain score at the Week 14 endpoint
- Change from baseline in the FIQR function domain score at the Week 14 endpoint
- Change from baseline in the Patient Reported Outcomes Measurement Information System (PROMIS) score for sleep disturbance at the Week 14 endpoint
- Change from baseline in the PROMIS score for fatigue at the Week 14 endpoint
- Change from baseline in the weekly average of the daily diary assessment of sleep quality at the Week 14 endpoint

7.2.3. Exploratory efficacy endpoints:

- Proportion of patients with a ≥30% improvement from baseline to Weeks 1-14 in the daily self-reported pain severity score
- Proportion of patients with a ≥50% improvement from baseline to Weeks 1-14 in the daily self-reported pain severity score
- Proportion of patients with a PGIC rating of "very much improved" or "much improved" at all post-randomization clinic visits
- Change from baseline in the FIQR total score, overall impact domain score, and individual item scores at all post-randomization clinic visits
- Change from baseline in the FIQR symptoms domain score and function domain scores at all post-randomization clinic visits
- Change from baseline in the PROMIS score for sleep disturbance and fatigue at all post-randomization clinic visits
- Change from baseline in the PROMIS score for fatigue at all 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 self-reported average pain severity score at Weeks 1-14
- Changes from baseline in patient-rated Changes in Sexual Functioning Questionnaire Short-Form (CSFQ-14) in females and in males, analyzed separately

Additional exploratory analyses may be defined in the Statistical Analysis Plan (SAP).

7.2.4. Safety

- Incidence of adverse events
- 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 the Columbia- Suicide Severity Rating Scale (C-SSRS) scale
- Changes from baseline in Beck Depression Inventory-II (BDI-II) scores

7.3. Number of Patients and Treatment Assignment

Approximately 470 patients will be randomized in a 1:1 ratio to treatment with TNX-102 SL 5.6 mg (2 x 2.8 mg tablets) or SL placebo tablets. Randomization will be stratified by center. Randomized patients who withdraw will not be replaced. Each patient will participate for 15-19 weeks in an outpatient clinic setting. This includes a variable 1 to 5-week screening and washout period, and a 14-week treatment period.

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 during the screening period:

1. The patient is male or female 18 to 65 years of age, inclusive.
2. The patient has a diagnosis of primary FM as defined by the 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria (American College of Rheumatology Preliminary Diagnostic Criteria), which includes all of the following:
    a. Generalized pain, defined as pain in at least 4 of 5 regions
    b. Symptoms have been present at a similar level for at least 3 months; and
    c. Widespread pain index (WPI) ≥7 and symptom severity scale (SSS) score ≥5; OR WPI between 4-6 and SSS scale score ≥9; and
    d. The patient does not have another disorder that would otherwise explain his/her pain.
3. The in-clinic 7-day recall NRS average daily pain intensity score at Screening Visit must be ≥ 4 and ≤ 9. Exceptions are only possible with Medical Monitor approval.
4. If female, is either not of childbearing potential (defined as postmenopausal for at least 1 year or surgically sterile [e.g., bilateral tubal ligation, bilateral oophorectomy, or hysterectomy]) or will be practicing one of the following methods of birth control throughout the study:
    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 (IUD);
    c. Double-barrier method (condoms, sponge, diaphragm, or vaginal ring with spermicidal jelly or cream);
    d. Partners of vasectomized males in stable relationships;
    e. Females involved in stable same sex relationships;
    f. Female patients practicing abstinence may have the birth control requirement waived only with Medical Monitor approval.
5. Patients currently receiving non-exclusionary pharmacologic treatment for depression should have been clinically stable for at least 3 months prior to randomization, and on stable doses of the antidepressant regimen during this 3-month time frame.
6. 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 formulations of cyclobenzaprine, and benzodiazepines.

7. The patient is willing and able to comply with all protocol-specified requirements.
8. The patient is capable of reading and understanding English and has provided written informed consent to participate. Separate written, signed informed consent will be required if the patient is to participate in the optional pharmacogenomic assessment. A decision not to participate in optional pharmacogenomic testing will not affect the patient's eligibility for the main study.
9. In addition to satisfying all other eligibility and randomization criteria, the patient has also received Medical Monitor Pre-Randomization Approval to proceed to the Baseline/Randomization visit.

8.3. Patient Exclusion Criteria

Eligible patients who meet any of the following criteria during the screening period should be excluded from the study:

1. The patient has been diagnosed with infectious or inflammatory arthritis (e.g., rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis), systemic lupus erythematosus, untreated or active gout, (i.e. any acute attack within past 2 years is exclusionary), or meets criteria for other type of systemic autoimmune disease.
2. The patient has been diagnosed with a complex regional pain syndrome, failed back surgery syndrome, persistent or prevalent pain symptoms related to systemic disease (e.g., diabetic peripheral neuropathy, post-herpetic neuropathy), untreated hyperparathyroidism, or a history of prior surgery, trauma or other source of pain that, in the Investigator's opinion, would confound or interfere with the assessment of the patient's fibromyalgia pain 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) and Module K (Psychotic 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). Any patient who scores ≥ 7 on the MSI-BPD may be randomized only with Medical Monitor approval.
5. The patient is at increased risk of suicide on the basis of the Investigator's judgment, or the results of the BDI-II (a response > 1 to BDI-II item #9), or the results of the C-SSRS conducted at Screening (e.g., any C-SSRS Type 3, 4 or 5 suicidal ideation during the preceding 6 months and any suicidal behavior within the past 12 months) and Baseline (e.g., any C-SSRS Type 3, 4, or 5 suicidal ideation or any suicidal behavior since Screening visit).
6. A BDI-II score greater than 24 at either the Screening or Baseline visit.
7. The patient has participated in any other study with TNX-102 SL.

8. Based on screening laboratory results, thyroid-stimulating hormone (TSH) > 1.5 times the upper limit of normal or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 times the upper limit of normal; 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 (e.g., significant arrhythmia; heart block; heart failure; symptomatic coronary artery disease), 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 has a known current clinically significant systemic infection (e.g., HIV, hepatitis).
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 or locally injected 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 EC#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 wash-out of the following medications during screening, or wash-out is inadvisable: monoamine oxidase inhibitors (30 days), levomilnacipran, anticonvulsants (except when used for migraine prophylaxis), amphetamine mixed salts, weight loss agents such as phentermine and diethylpropion, muscle relaxants (e.g., methocarbamol, baclofen, carisoprodol), stimulants (e.g., methylphenidate, lisdexamfetamine, dextroamphetamine), mirtazapine, trazodone, nefazodone, St. John's wort, any medication known to be a strong CYP3A4 inhibitor (Appendix 1), or any of the medications listed in Inclusion Criterion #6.
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, or interfere with 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 known hypersensitivity to cyclobenzaprine or the excipients in TNX-102 SL or placebo formulations.
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 (e.g., apnea/hypopnea index 5-15), and/or patients whose mild to moderate sleep apnea is well-controlled with CPAP or oral device, are allowed at the discretion of the Investigator. Due to the increased risk of sleep apnea, any patient with a body mass index (BMI) >45 must receive Medical Monitor approval prior to randomization.
25. The patient has a history of narcolepsy, cataplexy, periodic involuntary limb movement disorder or other documented, clinically significant sleep disorder.
26. Patient has plans for international travel, or has a work schedule (e.g., requiring night shifts), that prevents them from being able to utilize the diary system during its available time window or to take study drug on a regular basis.
27. The patient is currently being treated with sodium oxybate or ketamine or calcitonin gene-related peptide (CGRP) receptor antagonists.
28. The patient is currently filing or seeking a work disability claim for any reason or condition.
29. The patient has received an investigational calcitonin gene-related peptide (CGRP) receptor antagonist within 90 days of Screening, or any other investigational drug within 30 days of Screening.

8.4. Randomization Criteria

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 FM pain satisfies the following criteria, as assessed by diary pain scores (24 hour recall):
    a. A mean 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 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. Pain scores recorded on at least 5 out of the 7 days immediately preceding Visit 2.

If the patient does not satisfy these randomization criteria, the patient has failed to qualify for this study and should be considered a screen failure, with the reason documented. With Medical Monitor approval, if the patient is otherwise considered a qualified and compliant patient, Visit 2 may be delayed for up to 7 days to accommodate situations in which the patient has been unable to record 5 of 7 days of pain scores due to acceptable extenuating circumstances. There is no requirement for a Follow-Up visit for screen failures.

8.5. Patient Withdrawal Criteria

In accordance with the Declaration of Helsinki, human subjects 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 11.5.2.

9. TREATMENT OF PATIENTS

9.1. Prior and Concomitant Medications

Patients who are taking certain medications to manage their FM are eligible for the study if they are willing and able (and it is medically reasonable for them) to be withdrawn from those medications that are specifically excluded by the protocol and they agree to refrain from further usage during this study. The specific medications that must be withdrawn include milnacipran, pregabalin, duloxetine, tramadol, gabapentin, any form of cyclobenzaprine (AMRIX®, FEXMID® or generic cyclobenzaprine), tapentadol, amitriptyline and other tricyclic antidepressants, trazodone, narcotics/opioids and naltrexone (including CONTRAVE®). In addition, certain other medications are prohibited and may require washout, or exclusion of patients for whom washout is not appropriate (e.g., benzodiazepines, anticonvulsants (except when used as migraine prophylaxis), levomilnacipran, mirtazapine, nefazodone, St. John's wort, phentermine, diethylproprion, muscle relaxants (e.g., methocarbamol, baclofen, carisoprodol), and systemic use of strong CYP3A4 inhibitors as defined in Appendix 1 (i.e., topical use is not excluded).

All patients undergoing washout must complete a 3-week drug-free interval prior to the Baseline/Randomization visit (Visit 2); this will provide two weeks of washout prior to the 7 days leading up to Visit 2 when baseline efficacy data will be collected on the daily diary. Any patient with a positive screening UDS who is washing off an opioid, amphetamine, or benzodiazepine must return to the clinic for a repeat UDS before they begin their 7-day baseline data collection period leading up to Visit 2.

In general, patients utilizing benzodiazepines on a chronic or regular basis should not be considered for the study; however, washout may be considered for those patients utilizing them only on an occasional or as-needed basis (e.g, three times per week or less, on average). In addition, patients taking benzodiazepines for restless leg syndrome should not be considered, since washout would not be advised. Buspirone, however, is allowed.

Several benzodiazepines are not easily detected by the in-clinic urine dipstick; therefore, patients positive for benzodiazepines at Screening and deemed appropriate for washout will require a centrally-interpreted repeat UDS conducted prior to the beginning of the 7-day baseline data collection period prior to V2. All other repeat urine drug screens can be conducted on-site. All repeat UDS results must be confirmed negative before the patient can be randomized.

Patients using non-benzodiazepine hypnotics (e.g., zolpidem, eszopiclone, zaleplon) on a chronic, nightly basis should not be enrolled; however, patients utilizing these medications on an infrequent or occasional basis only (e.g., three times per week or less, on average) may be considered. Similar to the benzodiazepines, drugs in this class of medication can negatively impact sleep architecture; therefore, patients utilizing either non-benzodiazepines or benzodiazepines should be discussed with the Medical Monitor early during the screening process to determine their suitability for the study and to determine whether washout is clinically advisable. Patients washing off non-benzodiazepines should not be randomized if they are unable to discontinue their use and remain drug-free through their 7-day baseline data collection period leading up to Visit 2. The patient's ability to successfully discontinue their use of

excluded sleep therapies should be carefully assessed, since UDS testing is not available for non-benzodiazepine hypnotics.

After randomization, sedating antihistamines (e.g., diphenhydramine, hydroxyzine) may be used as needed for insomnia; however, patients will need to refrain from their use during the week of baseline data collection leading up to Visit 2. Patients should track their use of sedating antihistamines in between study visits so that changes in usage during the course of the study can be tracked and recorded.

The use of melatonin, ramelteon, and valerian root is not restricted. Similarly, the use of cannabidiol (CBD) products is not restricted, but like all other allowed concomitant medications, its usage should have been stable for at least 30 days prior to randomization, and usage should remain stable during the study. Additionally, the use of CBD products should not be started after randomization. All CBD products should be added to the concomitant medication source and case report form (CRF).

Due to the exclusion of all opioids 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 with neuropathic pain in addition to fibromyalgia should not be washed off of gabapentin, pregabalin or any other anticonvulsant, and therefore should not be considered for the study.

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 withdrawal must be accomplished so that the patient is medication free for at least 21 days prior to randomization. This will provide 14 days off the excluded medication before the patient starts the 7-day run-in phase during which critical baseline efficacy data are collected by means of the daily diary. Any additional time required for down-titration would be in addition to this 21-day washout requirement. For this reason, patients can remain in screening for up to 35 days, which provides an additional 2 weeks for down-titration, if required. For extenuating circumstances, the duration of the Screening period may be increased to up to 49 days with Medical Monitor approval.

Other chronic prescription or over-the-counter medication not specifically excluded by an exclusion criterion may be continued in the study, provided that the patient has been on this medication for at least 30 days at a stable dose (except for allowed antidepressants, which require 90 days at stable dose) from the date of randomization, and usage is expected to remain stable throughout the study. Allowed medications include, but are not limited to, hormonal therapy (contraceptives and replacement therapy), anti-hypertensive agents, lipid-lowering medications, selective serotonin reuptake inhibitors (SSRI) and other allowed antidepressants (e.g., venlafaxine, desvenlafaxine, bupropion, vilazodone).

Acetaminophen (up to 3000 mg/day) and non-steroidal anti-inflammatory drugs (NSAIDs) may be continued in a stable fashion for osteoarthritis or other allowed indications (e.g., aspirin for cardioprophylaxis), or used as needed for other sources of acute, minor pain. Note that acetaminophen and NSAIDs may be taken either on a regular basis, or on an as-needed (prn) basis; however, if used as-needed, the Investigator should ascertain the patient's typical pattern of usage (e.g., average dosage and frequency per defined time interval) so that this information can be recorded on the CRF. Any significant change in the patient's usage of any medication,

including those taken only as needed, should result in an update to the CRF. The CRF entry for any prn medication is expected to include an estimation of the patient's average dosage and frequency per defined time interval.

Patients on allowed antidepressants due to a history of depression should only be considered for the study if no changes in antidepressant agent or dose have occurred during the 90 days leading up to randomization, and no changes are anticipated or planned during the treatment phase of the study. In addition, FM patients with comorbid depression who are being treated with duloxetine, milnacipran, levomilnacipran, monoamine oxidase inhibitors, or tricyclic antidepressants should in general not be considered for the study since washout of these agents could destabilize their psychiatric status.

NOTE: Participating patients receiving treatment with antidepressants should be cautioned about the possibility of serotonin syndrome, which has been reported in patients receiving cyclobenzaprine with SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRI) and related agents. This will be included in the ICF.

New medications that are deemed required, in the opinion of the Principal Investigator or another physician, will be allowed, including medications needed to treat adverse events. After randomization, if there is a requirement for treatment with an acute opioid or other treatment that may confound the evaluation of pain at critical times during the study (defined as the week prior to Visits 3, 4, 5 or 6), 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 these visits. While it is understood that opioid usage will occasionally be necessary and unavoidable, it could have consequences on the patient's data.

Similarly, if there is a requirement for acute, short-term opioid usage during the screening phase, the start of the 7-day run-in phase should be delayed to ensure at least 2 days between the last opioid dose and the beginning of the 7-day run-in phase. In other words, there may be some circumstances when the unexpected requirement for short-term opioid usage, specifically due to an *acute* medical, dental or surgical condition, does not require the full 21-day washout. This provision only applies to *acute* pain conditions – not to opioid usage due to a flare in patient's FM or other chronic pain condition. Any requirement for acute opioid usage during the screening phase should be brought to the attention of the Medical Monitor to ensure adequate washout prior to randomization.

Patients should refrain from drinking grapefruit juice or eating grapefruit during the study due to its ability to inhibit CYP3A4 activity. Aside from this restriction, there are no other food or fluid restrictions in this study except for the instructions pertaining to dosing (Section 10.2).

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.

Any concomitant medications or other treatments must be recorded in the patient's medical record and case report form along with the dose and dates of treatment.

9.2. Cannabis/THC Use

Patients utilizing cannabis/THC are to be excluded if MINI 7.0.2 criteria are met for greater than MILD Cannabis Use Disorder during the preceding 12 months (prior to the Screening visit), 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. Cannabis/THC 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. If study drugs are to be withdrawn for the explicit purpose of participation in this study, the patient must have already provided consent and signed an informed consent form before the withdrawal or down titration of any drug 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-F304, sponsor name and address, bottle number, quantity, storage conditions, usage instructions, and caution statements for investigational new drug, i.e., 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 two bottles will be dispensed at Visit 3 (Week 2), Visit 4 (Week 6), and Visit 5 (Week 10). Study drug will be mailed via courier to a patient's home where a telephone visit is scheduled to be conducted. 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[1]; 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, brief excursions (15-30°C/59-86°F) as defined in the Study Reference Manual (Investigational Product Receipt and Storage) are permitted without the sponsor's approval.

10.2. Dosing Instructions

Patients will be instructed to take 1 tablet of randomly assigned study drug TNX-102 SL 2.8 mg or SL 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 one or two SL tablets under their tongue (if two, 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 or drink (or chew gum) for at least 15 minutes after dosing, and preferably not to drink any hot, cold or acidic beverage until

[1] All references to a site/study center visit for Weeks 2, 6, 10, and 14 include telephone visits for Weeks 2, 6, and 10, and home visits or telephone visit for Week 14/ET that are being allowed due to the circumstances of the COVID-19 pandemic.

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 (two) tablets are allowed per day. Note: In the event that the patient misses a dose, instruct the patient to continue dosing with two (2) tablets the next evening; i.e., 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 one tablet sublingually nightly. Any reduction in study drug dose must be carefully documented in the 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 two TNX-102 SL tablets daily at bedtime). [redacted]

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 before bedtime for the first 2 weeks.

Study treatments 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.

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

In the event of loss of a study drug bottle, 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), unless a telephone visit, where patients will be asked to count the number of tablets remaining in their current bottles, document this on a form provided to patient, and return this form and study drug (with bottles) via courier to the site. 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. For telephone visits, drug accountability by the site staff will occur after the study drug is returned to the site via courier. For home visits (Week 14 or ET only), site staff will collect bottles and conduct accountability upon return to the site. 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 one of the Medical Monitors should be contacted.

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 (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 informed consent form. This signed informed consent form 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 informed consent form. The patient will be required to sign all updated informed consents.

11.1.2. Screening Overview

The first study visit, Screening Visit 1, will be where the study is explained to the prospective study patient, where written informed consent will be obtained and documented, and where certain protocol-specified study procedures and assessments will be completed. Screening Visit 1 will start a variable length screening period. The length of the screening 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 wash-out 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 wash-out, 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 (e.g. 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 wash-out 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 (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
- Inclusion/exclusion criteria
- Demographics
- Medical history
- Confirmation that patient satisfies the 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria (2010 American College of Rheumatology provisional diagnostic criteria/2011 self-report modification for survey and clinical research)
- Prior medication history
- Lifetime fibromyalgia pharmacotherapy history
- NRS assessment of 7-day recall of average daily pain. Patients should only continue screening if they score ≥4 and ≤9. A score outside this range will require Medical Monitor approval in order to continue.
- 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), and K (Psychotic Disorders)
- MSI-BPD
- BDI-II. Any patient with a BDI-II total score > 24 or a response of 2 or 3 to item #9 (suicidal ideation) is not eligible for randomization.
- "Baseline/Screening" version of the C-SSRS. Any patient with C-SSRS Type 4 or 5 ideation during the preceding 6 months or any suicidal behavior during the preceding 12 months should be screen failed.
    a. Results of the C-SSRS and BDI-II should be reviewed together at each visit to ensure (1) the patient is not experiencing suicidal ideation or worsening depression that requires intervention and (2) both scales are providing a consistent clinical picture of the patient with regard to suicidality.
- Physical examination, including vital signs, height, weight and BMI. Patients with BMI>45 must receive Medical Monitor approval prior to randomization.
- 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.

- Clinical laboratory tests
- Drug screening
- Serum pregnancy test (for women of child-bearing potential)
- 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 instructed regarding the questions that will be asked of them on the daily diary and 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 that are planning on international travel during the study period, or who work night shifts, should not be considered for the study.
    b. Receive an appointment to return to the clinic for Visit 2.
    c. Receive a schedule for down-titration (if required) of any prohibited medications to be discontinued.

11.2. Visit 2 (Baseline: Day 1)

Visit 2 should be scheduled after the patient has completed their medication wash-out 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, will undergo several baseline assessments at this visit, and 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 are eligible for randomization:

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

- Confirm patient's eligibility based on the diary data collected during the preceding 7 days
- Review completed diary data with the patient
- Update medical history (with any changes noted since screening)
- Assess changes in medication history and concomitant medications
- Have the patient complete the BDI-II. If the BDI score is >24, the patient is not eligible for randomization and should be screen failed. In addition, a score > 1 on item #9 (suicidal ideation) is exclusionary.
- 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.
    a. Results of the C-SSRS and BDI-II should be reviewed together to ensure (1) the patient is not experiencing suicidal ideation or worsening depression that requires intervention and (2) both scales are providing a consistent clinical picture of the patient with regard to suicidality.
- Assess occurrence of adverse events
- Conduct a brief physical examination, including vital signs and weight
- Conduct a visual examination of the oral cavity. 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.
- Perform urine pregnancy test (for women of child-bearing potential)
- Patient should complete the following patient-reported outcomes (PRO):
    a. FIQR
    b. Clinic administered assessment of pain by both 24-hour and weekly recall using 11-point (0-10) NRS scale
    c. PROMIS scales for sleep disturbance and fatigue
    d. CSFQ-14 female or male version, as appropriate
- Ensure that all PROs were accurately and fully completed

- Once it has been confirmed that the patient remains eligible, randomize patient via IRT Randomization System
- Dispense bottle of double-blind study drug as assigned via the IRT
- Review patient instructions regarding study drug dosing and diary completion (Section 10.2 and Section 12.2.6).

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 (e.g., 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 (i.e. extenuating circumstances due to COVID-19 pandemic), a telephone visit is an option. All assessments should be performed with exceptions of the ones specifically noted with comments in parenthesis.

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

- Review completed diary data and diary compliance with the patient
- Assess changes in medication history and concomitant medications

- 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).
- Have the patient complete the BDI-II
- Administer the "Since Last Visit" version of the C-SSRS
    a. Results of the C-SSRS and BDI-II should be reviewed together to ensure (1) the patient is not experiencing suicidal ideation or worsening depression that requires intervention and (2) both scales are providing a consistent clinical picture of the patient with regard to suicidality. (Telephone visit exception – response to Question #9 of the BDI-II is reviewed with the patient and C-SSRS is administered over the phone).
- Assess occurrence of adverse events
- 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. PGIC
    b. FIQR
    c. Clinic administered assessment of pain by both 24-hour and weekly recall using 11-point (0-10) NRS scale
    d. PROMIS scales for sleep disturbance and fatigue
- Ensure that all PROs were accurately and fully completed
- Vital signs (Telephone visit exception – vital signs are not required)
- 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, PI and Medical Monitor should also confer on whether study drug should be discontinued.)

- Discuss the scheduled increase in dose of study drug from one sublingual tablet (Days 1-14) to two 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 (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 and confirm that the increase in drug dosing to two tablets sublingually at bedtime is understood by patient
- Perform in-clinic urine pregnancy test (for women of child-bearing potential). (Telephone visit exception – urine pregnancy test will be performed at home by patient for women of child-bearing potential).

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. If this is a telephone visit, the patients will be instructed to return the PROs and study drug (and bottle) to the site via courier.

11.4. Visits 4 and 5

Visits 4 and 5 are similar study visits that are scheduled to be conducted after 6, and 10 weeks of treatment, respectively. Visit 4 should occur on Day 43 ±7 days and Visit 5 should occur on Day 71 ± 7 days. For those patients unable to return to the site (i.e. extenuating circumstances due to COVID-19 pandemic), a telephone visit is an option for both Visit 4 and Visit 5. All assessments should be performed with exceptions of the ones specifically noted with comments in parenthesis.

The following assessments and procedures are scheduled for these visits in the following general order:

- Review completed diary data and diary compliance with the patient
- Assess changes in medication history and concomitant medications
- Assess study drug compliance and collect previously dispensed study drug and bottles (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).
- Have the patient complete the BDI-II
- Administer the “Since Last Visit” version of the C-SSRS
    a. Results of the C-SSRS and BDI-II should be reviewed together to ensure (1) the patient is not experiencing suicidal ideation or worsening depression that requires

intervention and (2) both scales are providing a consistent clinical picture of the patient with regard to suicidality. (Telephone visit exception – response to Question #9 of the BDI-II is reviewed with the patient and C-SSRS is administered over the phone).

- Assess occurrence of adverse events
- 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. PGIC
  b. FIQR
  c. Clinic administered assessment of pain by both 24-hour and weekly recall using 11-point (0-10) NRS scale
  d. PROMIS scales for sleep disturbance and fatigue
- Ensure that all PROs were accurately and fully completed
- Vital signs (Telephone visit exception – vital signs are not required)
- 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, PI and Medical Monitor should also confer on whether study drug should be discontinued.)
- Dispense new bottles (unopened) of double-blind study drug as assigned by IRT (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 and drug dosing
- Perform in-clinic urine pregnancy test (for women of child-bearing potential) (Telephone visit exception – urine pregnancy test will be performed at home by patient for women of child-bearing potential).

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 study drug back to the

clinic at their next visit. If this is a telephone visit, the patients will be instructed to return the PROs and study drug (and bottles) to the site via courier.

11.5. Visit 6 (Week 14 or Early Termination)

11.5.1. 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.

- Assess changes in medication history and concomitant medications
- Assess study drug compliance and collect previously dispensed study drug and bottles (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).
- Have patient complete the BDI-II
- Administer the "Since Last Visit" version of the C-SSRS
    a. Results of the C-SSRS and BDI-II should be reviewed together at each visit to ensure (1) the patient is not experiencing suicidal ideation or worsening depression that requires intervention and (2) both scales are providing a consistent clinical picture of the patient with regard to suicidality. (Telephone visit exception – response to Question #9 of the BDI-II is reviewed with the patient and C-SSRS is administered over the phone).
- Assess occurrence of adverse events
- Have 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. PGIC

b. FIQR

c. Clinic administered assessment of pain by both 24-hour and weekly recall using 11-point (0-10) NRS scale

d. PROMIS scales for sleep disturbance and fatigue

e. CSFQ-14 female or male version, as appropriate

- Ensure that all PROs were accurately and fully completed
- Brief physical examination, including vital signs, weight (Telephone visit exception – brief physical exam, vital signs, and weight are not required)
- 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.)
- Obtain blood for clinical laboratory tests (Telephone visit exception – laboratory tests are not required).
- Perform in-clinic urine pregnancy test (for women of child-bearing potential) (Telephone visit exception – urine pregnancy test will be performed at home by patient for women of child-bearing potential).

11.5.2. 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 Early Termination Visit. The purpose of the Early Termination 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
- Assess changes in medication history and concomitant medications
- Assess study drug compliance (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).
- Have patient complete the BDI-II
- Administer the "Since Last Visit" version of the C-SSRS
    a. Results of the C-SSRS and BDI-II should be reviewed together to ensure (1) the patient is not experiencing suicidal ideation or worsening depression that requires intervention and (2) both scales are providing a consistent clinical picture of the patient with regard to suicidality. (Telephone visit exception – response to Question #9 of the BDI-II is reviewed with the patient and C-SSRS is administered over the phone).
- Assess occurrence of adverse events
- 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. PGIC
    b. FIQR
    c. Clinic administered assessment of pain by both 24-hour and weekly recall using 11-point (0-10) NRS scale
    d. PROMIS scales for sleep disturbance and fatigue
    e. CSFQ-14 female or male version, as appropriate
- Brief physical examination, including vital signs, weight (Telephone visit exception – brief physical exam, vital signs, and weight are not required)
- Inspection 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.)

- Obtain blood for clinical laboratory tests (Telephone visit exception – laboratory tests are not required).
- Perform in-clinic urine pregnancy test (for women of child-bearing potential) (Telephone visit exception – urine pregnancy test will be performed at home by patient for women of child-bearing potential).

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 adverse event or other condition.

11.6. 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.

12. STUDY ASSESSMENTS

12.1. Screening Assessments Not Discussed Elsewhere

12.1.1. Diagnosis of Fibromyalgia (2016 Revisions to the 2010/2011 Fibromyalgia Diagnostic Criteria)

The patient is eligible for this study if he/she has a diagnosis of primary FM as defined by the 2016 Revisions to the 2010/2011 Fibromyalgia Diagnostic Criteria (2010 American College of Rheumatology provisional diagnostic criteria/2011 self-report modification for survey and clinical research) (Wolfe et al, 2016) (Inclusion Criterion # 2). This diagnosis is determined by satisfaction of all of the following:

- Generalized pain, defined as pain in at least 4 of 5 regions, and
- Symptoms have been present at a similar level for at least 3 months; and
- WPI score ≥7 and SSS score ≥5; OR WPI between 4-6 and SSS score ≥9
- The patient does not have another disorder that would otherwise explain his/her pain.

The 2016 Fibromyalgia Diagnostic Criteria will be assessed at Visit 1.

12.1.2. 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 (e.g., significant arrhythmias or heart block, left bundle branch block (LBBB), 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.

12.2. Efficacy Assessments

The primary efficacy endpoint and many of the secondary and exploratory efficacy endpoints in this study are derived from subjective 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.

12.2.1. Daily 24-hour pain recall using 11-point Numerical Rating Scale (NRS)

Patients will provide a numeric assessment of their pain (24-hour recall), via the diary, using an 11-point (0=no pain to 10=worst possible pain) NRS scale. Patients will be asked to complete this assessment on a daily basis during the pre-treatment run-in period and throughout the

double-blind treatment period. Additional information regarding the patient diary is provided in Section 12.2.6.

12.2.2. Patient Global Impression of Change (PGIC)

The PGIC is a FM-specific validated instrument to gauge the patient's assessment of change in condition. This form will be completed by the patient at Visits 3, 4, 5 and 6. The patient will answer a single question:

Since the start of the study, overall my fibromyalgia is:

1 = Very much improved
2 = Much improved
3 = Minimally improved
4 = No change
5 = Minimally worse
6 = Much worse
7 = Very much worse

12.2.3. Fibromyalgia Impact Questionnaire - Revised (FIQR)

The patient's total score on the Fibromyalgia Impact Questionnaire (revised version) will be assessed at Visits 2, 3, 4, 5 and 6. The FIQR is made up of 3 domains: functional (9 questions), overall impact (2 questions) and symptoms (10 questions).

12.2.4. Clinic Assessment of Pain (24-hour and weekly recall)

In addition to the diary assessments of 24-hour pain recall (Section 12.2.1), patients will be asked to rate their average pain on paper using the 11-point (0-10) NRS scale at Visits 2, 3, 4, 5 and 6 using both a 24-hour and 7-day recall interval. There is no requirement to reconcile the pain responses obtained from these paper assessments to the 24-hour daily diary assessments.

12.2.5. 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.

Two PROMIS Scales will be assessed in this study, including the sleep disturbance scale (version 8a) and the fatigue scale (version 8a). Each of these two scales will be assessed at Visits 2, 3, 4, 5 and 6.

12.2.6. Diary Assessments

The daily diary 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 need to receive instructions and a password that uniquely identifies them when they log into the 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 average pain during the past 24 hours on a scale from 0-10, where zero is no pain and 10 is worst possible pain.
- 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)

The study staff will be expected to monitor patient adherence in completing the diary throughout the study, and will be instructed to call the patient should any problems or significant non-adherence 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 who have been randomized should be encouraged to continue to complete their diary. Patients will receive a reminder to complete their diary if they miss diary entries. Patients who miss two 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.

12.2.7. Assessment of Changes in Sexual Function: Changes in Sexual Functioning Questionnaire Short-Form (CSFQ-14)

The CSFQ-14 (Keller et al. 2006) is validated scale with internal reliability designed to allow a patient to self-evaluate his or her sexual behaviors or problems in a number of areas. The CSFQ-14 will be administered at Baseline (Visit 2) and Week 14/ET (Visit 6). It yields a total score, three subscales corresponding to phases of the sexual response cycle (i.e. desire, arousal, orgasm), and five subscales corresponding to important dimensions of sexual functioning. It is considered a useful scale for assessing sexual side effects of medications. For all items, higher scores reflect higher sexual functioning. For 12 of the 14 items, higher sexual functioning corresponds to greater frequency or enjoyment/pleasure (e.g. 1=never to 5 = every day). For two items (item 10, assessing loss of interest after arousal for women and priapism for men, and item 14, assessing painful orgasm), higher sexual functioning corresponds to lower frequency (e.g. 1=every day; 5=never). Items 10 and 14 are included in the total score but not in any subscale scores.

12.3. Safety Assessments

Safety will be assessed by evaluation of adverse events, vital signs, responses on the Columbia-Suicide Severity Rating Scale, responses on the BDI-II, and by clinical laboratory and physical examination findings, including visual inspection of the oral cavity.

12.3.1. Adverse Events

Patients will be monitored for AEs throughout the study. Any clinically significant abnormal findings at screening should be recorded in medical history. Adverse Events 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.

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 fibromyalgia 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 adverse events.

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

12.3.2. 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 adverse event, 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.

12.3.3. Beck Depression Inventory (BDI-II)

The BDI-II is a 21-item measure of the severity of current depressive symptoms, extensively validated for use in both medical and mental health populations. While this instrument does not provide a psychiatric diagnosis of depression, it does provide a continuous scale for measuring the severity of depressive symptomatology. Scoring allows for the identification of mild, moderate, and severe levels of depressive symptoms, and for the quantification of change in status over time.

The patient will be asked to complete this questionnaire at all in-clinic study visits, and for all telephone visits. The BDI-II will be sent by courier to the patient in advance of the phone call. At Visit 1 and Visit 2, patients whose responses are indicative of suicidal ideation, as defined by a response to Item #9 of >1, will be excluded from participation, and appropriate intervention prescribed. In addition, patients whose total BDI score is > 24 at either Visit 1 or Visit 2 will not be eligible for randomization and should be screen failed (and referred for appropriate psychological evaluation or care, if indicated). After Visit 1, the responses to Question #9 should be monitored to ensure that there is no increase in suicidal ideation during the study (and to assess correlation with C-SSRS findings) and the total score also followed to ensure the patient's psychological status remains stable.

12.3.4. 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 Columbia-Suicide Severity Rating Scale 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 (e.g., 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". Note that if there has been a significant change in responses indicative of increased suicide risk, appropriate intervention should be prescribed.

12.3.5. 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, oral temperature, and weight) will be assessed at Visits 1, 2, 3, 4, 5 and 6 (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).

12.3.6. 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.

12.3.7. 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 Screening Visit 1 and at Visit 6 (Week 14) or Early Termination, aside from urine pregnancy tests and ad hoc urine drug screens.

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 urine drug screen (UDS) will be performed at Visit 1. If the patient has a positive drug screen at Visit 1 due to a drug of abuse (e.g., 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 (e.g., 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, or ALT or AST level > 2 times the upper limit of normal, is exclusionary; however, the patient may remain in screening to undergo repeat LFT 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]	MCH concentration (MCHC)
Bicarbonate	Mean corpuscular hemoglobin (MCH)
Bilirubin (direct and total)	Mean corpuscular volume (MCV)
Blood urea nitrogen (BUN)	Platelet count
Calcium	Red blood cell (RBC) count
Chloride	WBC differential
Cholesterol (total)	Neutrophil count (absolute and %)
Creatine kinase (CK)	Lymphocyte count (absolute and %)
Creatinine	Monocyte count (absolute and %)
Glucose	Eosinophil count (absolute and %)
LDH	Basophil count (absolute and %)
Phosphorus	White blood cell (WBC) count
Potassium	Red blood cell distribution width (RDW)
Protein (albumin and total)	
Sodium	
HbA1c only if glucose > 180 mg/dL	
Thyroid-stimulating hormone (TSH) [c] at screening	Serum Pregnancy Test at Screening[b]
Free T4 only if TSH is outside of normal limits	Urine Pregnancy Test (qualitative dipstick)[b]
Pharmacogenomic testing (optional; can be obtained at any visit post-Screening, including an Early Termination visit)	Urine Drug Screen[d]

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

[b] 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).

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

[d] 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.

12.3.8. Pharmacogenomics Testing

For pharmacogenomic analysis, a single blood draw collected in one PAXgene DNA tube will be obtained from each patient after they have provided separate written, signed informed consent for pharmacogenomic analysis. Due to circumstances caused by the COVID-19 pandemic and 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). The purpose of this testing is to allow exome sequencing and analysis for genetic variants related to treatment response to TNX-102 SL. It is presumed that unused extracted DNA sample will be stored up to fifteen years, and potentially utilized to develop a pharmacogenomic test for determining 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 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.

Unless otherwise noted, significance tests of treatment differences will be tested at the two-sided 0.05 level.

13.1. Populations for Analysis

The following analysis populations are planned for this study:

- 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.

13.2. Estimate of 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 5.6 mg and placebo arms. [redacted]

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, MINI modules (A, C, I, J, K) diagnoses, and 2016 Revised 2010/2011 FM Diagnostic criteria 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. Efficacy Endpoints

Primary Efficacy Endpoint:

- Change from Baseline to the Week 14 endpoint in the diary NRS weekly average of daily self-reported average pain severity scores.

Secondary Efficacy Endpoints:

The six secondary efficacy endpoints listed below are considered key secondary endpoints and will be tested in that order:

- Proportion of patients with a PGIC rating of "very much improved" or "much improved" at the Week 14 endpoint
- Change from baseline in the FIQR symptoms domain score at the Week 14 endpoint
- Change from baseline in the FIQR function domain score at the Week 14 endpoint
- Change from baseline in the PROMIS score for sleep disturbance at the Week 14 endpoint
- Change from baseline in the PROMIS score for fatigue at the Week 14 endpoint
- Change from baseline in the weekly average of the daily diary assessment of sleep quality at the Week 14 endpoint

Exploratory efficacy endpoints:

- Proportion of patients with a ≥30% improvement from baseline to Weeks 1-14 in the daily self-reported average pain severity score
- Proportion of patients with a ≥50% improvement from baseline to Weeks 1-14 in the daily self-reported average pain severity scores
- Proportion of patients with a PGIC rating of "very much improved" or "much improved" at all post-randomization clinic visits
- Change from baseline in the FIQR total score, overall impact domain score, and individual item scores at all post-randomization clinic visits
- Change from baseline in the FIQR symptoms domain score and function domain scores at all post-randomization clinic visits
- Change from baseline in the PROMIS score for sleep disturbance at all post-randomization clinic visits
- Change from baseline in the PROMIS score for fatigue at all 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 self-reported average pain severity scores at Weeks 1-14
- Changes from baseline in patient-rated Changes in Sexual Functioning Questionnaire Short-Form (CSFQ-14) in females and in males, analyzed separately

13.4.2. Primary Efficacy Analysis

The primary efficacy parameter will be the contrast between active and placebo in the weekly mean change from baseline pain score at the Week 14 endpoint. The weekly pain score will be

based on the weekly average of the daily patient self-reported 24-hour recall average pain severity scores using an 11-point (0-10) NRS.

The primary ITT analysis will provide an estimate of 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 average pain severity 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 MMRM approach with multiple imputation for missing data. Covariates in the model will include the fixed categorical effects of treatment, center, 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 SAP for more details on the primary and secondary analyses.

13.4.3. 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.

13.4.4. Secondary Efficacy Analyses

Secondary efficacy analyses will be based on the ITT population only. For PGIC, patients with a "very much improved" or "much improved" response at the Week 14 endpoint will be considered responders. Patients with results in any other category or who discontinue early will be considered non-responders. PGIC responder status (yes/no) will be analysed using logistic regression with treatment and site as categorical effects. In addition, odds ratios and corresponding 95% confidence intervals will be presented.

Analysis of continuous secondary endpoints and adjustments for missing data will be described in detail in the SAP. Significance tests of treatment differences will be tested at the two-sided 0.05 level and corresponding 95% confidence intervals will be calculated.

To adjust for multiplicity and to control for overall type I error, a sequential test procedure will be applied to the efficacy endpoints. If the primary analysis produces a result that is statistically significant at the 0.05 level, a significance level of 0.05 will be used for comparing the secondary endpoints in an ordered fashion. If the analysis for a secondary endpoint does not produce a statistically significant result at the 0.05 level, then the remaining secondary endpoint analyses will automatically be considered non-significant regardless of the p-value produced. The order in which the 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.

13.4.5. Exploratory Efficacy Analyses

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

13.5. 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 Adverse Events
- 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
- Changes from baseline in BDI-II scores

All AEs, treatment-emergent adverse events (TEAE), and serious adverse events (SAE) 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 on-treatment 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 (mean, SD, median, minimum, and maximum) of actual values and changes from baseline at each assessment time point and last on-treatment assessment will be calculated for vital signs including weight, BMI, body temperature, pulse rate, systolic blood pressure and diastolic blood pressure. 95% 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 visit will be summarized by visit and treatment group. Additionally, the overall number of patients with any suicidal ideation or behavior (by type and in total) or self-injurious behavior while on-treatment will be provided by treatment group. Patients will only be counted once for on-treatment at the worst-case response for each item.

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

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from baseline at each assessment time point and last on-treatment assessment will be calculated for BDI-II scores. 95% confidence intervals will be presented for change from baseline.

13.6. Interim Analyses

An interim analysis will be performed once 50% of the planned patients have enrolled and those patients have either completed or discontinued the study. The purpose of the interim will be to potentially increase the sample size to maintain statistical power conditioned on the results of the first 50% of patients; or continue as planned if conditional probability of success at Week 14 is above a pre-specified threshold; or to stop the study early for success or for futility if the conditional power is sufficiently low. The study team will only be informed of the recommendation to maintain the original sample size, increase the sample size (by a fixed, pre-specified amount) or discontinue the study for success or for failure (at which point unblinding would occur).

For the primary and key secondary outcomes, the results from before and after the interim will be combined with Cui, Hung, Wang (CHW) methodology (Cui et al, 1999). Full details of the interim analysis will be included in the SAP and 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 Conference on Harmonization (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 subject 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® will be used as the standard coding dictionary for AEs and in describing the patient's medical history, and the World Health Organization (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.

A serious adverse event (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 and e-mail reports must be confirmed promptly either by facsimile or by email. For reporting SAEs, Tonix's designated Medical Monitor should be called, and the relevant forms submitted to [redacted] PV within 24 hours of the site's awareness of the SAE. The contact information for the Medical Monitor is as follows:

The Investigator, or the sponsor or designee in the case of a central 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 Interactive Response Technology 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 (See Appendix 2 for AMRIX® Package Insert). 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 (i.e., birth or voluntary or spontaneous termination of the pregnancy). 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 enter 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), any EC 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 informed consent forms, 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 Subjects," 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, 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 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 subjects/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 (SOPs) 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 subject 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 which 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 contract research organization 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 is collected via paper (patient questionnaires, etc.), the data must be entered into the eCRF 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 (e.g., written informed consent forms). 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 towards 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 sixty (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. LIST OF REFERENCES

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20. APPENDICES

APPENDIX 1 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 Sept. 26, 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 2 AMRIX® Package Insert (DATED April 2019)

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AMRIX safely and effectively. See full prescribing information for AMRIX.

AMRIX® (cyclobenzaprine hydrochloride extended-release capsules), for oral use
Initial U.S. Approval: 1977

INDICATIONS AND USAGE

AMRIX is a muscle relaxant indicated as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions. (1)

Limitations of Use:

- AMRIX should be used only for short periods (up to 2 or 3 weeks) (1)
- AMRIX has not been found effective in the treatment of spasticity or cerebral palsy (1)

DOSAGE AND ADMINISTRATION

- Recommended adult dose for most patients is 15 mg taken once daily. Some patients may require 30 mg taken once daily (2)
- Recommended to take doses at approximately same time each day (2)
- Instruct patients to swallow AMRIX capsules intact or to sprinkle capsule contents on a tablespoon of applesauce and swallow immediately without chewing (2)
- Use for periods longer than 2 or 3 weeks is not recommended (2)

DOSAGE FORMS AND STRENGTHS

- Extended-release capsules: 15 and 30 mg (3)

CONTRAINDICATIONS

- Hypersensitivity to any component of this product (4)
- Concomitant use of monoamine oxidase (MAO) inhibitors or within 14 days after their discontinuation (4)
- During acute recovery phase of myocardial infarction, and in patients with arrhythmias, heart block or conduction disturbances, or congestive heart failure (4)
- Hyperthyroidism (4)

AMRIX® (cyclobenzaprine hydrochloride extended-release capsules)

WARNINGS AND PRECAUTIONS

- Serotonin syndrome has been reported with cyclobenzaprine when used in combination with other serotonergic drugs (5.1)
- Cyclobenzaprine is structurally related to tricyclic antidepressants which have been reported to produce adverse cardiovascular effects or CNS depressant effects (5.2)
- Use in the elderly is not recommended (5.3)
- Use in patients with hepatic impairment is not recommended (5.4)
- Use with caution in patients with a history of urinary retention, angle-closure glaucoma, increased intraocular pressure and in patients taking anticholinergic medications (5.5)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥3% in any treatment group and greater than placebo): dry mouth, dizziness, fatigue, constipation, nausea, dyspepsia, and somnolence (6)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-888-483-8279 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- MAO Inhibitors: Life-threatening interactions may occur (4, 7)
- Serotonergic Drugs: Serotonin syndrome has been reported (5.1, 7)
- CNS Depressants: Effects of alcohol, barbiturates, and other CNS depressants may be enhanced (5.2, 7)
- Tramadol: Seizure risk may be enhanced (7)
- Guanethidine: Antihypertensive effect may be blocked (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 4/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

AMRIX® (cyclobenzaprine hydrochloride extended-release capsules) is indicated as an adjunct to rest and physical therapy for relief of muscle spasm associated with acute, painful musculoskeletal conditions. Improvement is manifested by relief of muscle spasm and its associated signs and symptoms, namely, pain, tenderness, and limitation of motion.

Limitations of Use:

- AMRIX should be used only for short periods (up to two or three weeks) because adequate evidence of effectiveness for more prolonged use is not available and because muscle spasm associated with acute, painful musculoskeletal conditions is generally of short duration and specific therapy for longer periods is seldom warranted.
- AMRIX has not been found effective in the treatment of spasticity associated with cerebral or spinal cord disease or in children with cerebral palsy.

2 DOSAGE AND ADMINISTRATION

The recommended adult dose for most patients is one (1) AMRIX 15 mg capsule taken once daily. Some patients may require up to 30 mg/day, given as one (1) AMRIX 30 mg capsule taken once daily or as two (2) AMRIX 15 mg capsules taken once daily.

- It is recommended that doses be taken at approximately the same time each day.
- Use of AMRIX for periods longer than two or three weeks is not recommended *[see Indications and Usage (1)]*.

Instruct patients to swallow AMRIX capsules intact. Alternatively, the contents of the AMRIX capsule may be sprinkled over applesauce and then swallowed. This method is appropriate only for patients able to reliably swallow the applesauce without chewing. Other foods have not been tested and should not be substituted for applesauce. Instruct the patient to:

- Sprinkle the contents of the capsule onto a tablespoon of applesauce and consume immediately without chewing.
- Rinse the mouth to ensure all of the contents have been swallowed.
- Discard any unused portion of the AMRIX capsules after the contents have been sprinkled on applesauce.

3 DOSAGE FORMS AND STRENGTHS

Extended-release capsules in the following strengths:

- 15 mg: Capsules are orange/orange and are embossed in blue ink with "15 mg" on the body, and Cephalon "C" logo, "Cephalon," and a dashed band on the cap.
- 30 mg: Capsules are blue/red and are embossed in white ink with "30 mg" on the body, and Cephalon "C" logo, "Cephalon," and a dashed band on the cap.

4 CONTRAINDICATIONS

- Hypersensitivity to any component of this product. These adverse reactions may manifest as an anaphylactic reaction, urticaria, facial and/or tongue swelling, or pruritus. Discontinue AMRIX if a hypersensitivity reaction is suspected.
- Concomitant use of monoamine oxidase (MAO) inhibitors or within 14 days after their discontinuation. Hyperpyretic crisis seizures and deaths have occurred in patients receiving cyclobenzaprine (or structurally similar tricyclic antidepressants) concomitantly with MAO inhibitor drugs.
- During the acute recovery phase of myocardial infarction, and in patients with arrhythmias, heart block or conduction disturbances, or congestive heart failure.
- Hyperthyroidism.

5 WARNINGS AND PRECAUTIONS

5.1 Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with cyclobenzaprine when used in combination with other drugs, such as selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), tramadol, bupropion, meperidine, verapamil, or MAO inhibitors. The concomitant use of AMRIX with MAO inhibitors is contraindicated *[see Contraindications (4)]*. Serotonin syndrome symptoms may include mental status changes (e.g., confusion, agitation, hallucinations), autonomic instability (e.g., diaphoresis, tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g., tremor, ataxia, hyperreflexia, clonus, muscle rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Treatment with AMRIX and any concomitant serotonergic agents should be discontinued immediately if the above reactions occur and supportive symptomatic treatment should be initiated. If concomitant treatment with AMRIX and other serotonergic drugs is clinically warranted, careful observation is advised, particularly during treatment initiation or dose increases.

5.2 Tricyclic Antidepressant-like Effects

Cyclobenzaprine is structurally related to the tricyclic antidepressants, e.g., amitriptyline and imipramine. Tricyclic antidepressants have been reported to produce arrhythmias, sinus tachycardia, prolongation of the conduction time leading to myocardial infarction and stroke *[see Contraindications (4)]*. AMRIX may enhance the effects of alcohol, barbiturates, and other CNS depressants.

Some of the more serious central nervous system (CNS) reactions noted with the tricyclic antidepressants have occurred in short-term studies of cyclobenzaprine for indications other than muscle spasm associated with acute musculoskeletal conditions, and usually at doses somewhat greater than those recommended for skeletal muscle spasm. If clinically significant CNS symptoms develop, consider discontinuation of AMRIX.

5.3 Use in the Elderly

As a result of a 40% increase in cyclobenzaprine plasma levels and a 56% increase in plasma half-life following administration of AMRIX in elderly subjects as compared to young adults, use of AMRIX is not recommended in the elderly *[see Clinical Pharmacology (12.3)]*.

5.4 Use in Patients with Hepatic Impairment

As a result of two-fold higher cyclobenzaprine plasma levels in subjects with mild hepatic impairment, as compared to healthy subjects, following administration of immediate-release cyclobenzaprine and because there is limited dosing flexibility with AMRIX, use of AMRIX is not recommended in patients with mild, moderate, or severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

5.5 Atropine-like Action

Because of its atropine-like action, AMRIX should be used with caution in patients with a history of urinary retention, angle-closure glaucoma, increased intraocular pressure, and in patients taking anticholinergic medication.

6 ADVERSE REACTIONS

The following clinically significant reactions are described in greater detail, in other sections.

- Serotonin Syndrome *[see Warnings and Precautions (5.1)]*
- Adverse Cardiovascular Effects *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described below reflect exposure to AMRIX in 253 patients in 2 clinical trials. AMRIX was studied in two double-blind, parallel-group, placebo-controlled, active-controlled trials of identical design *[see Clinical Studies (14)]*. The study population was composed of patients with muscle spasms associated with acute painful musculoskeletal conditions. Patients received 15 mg or 30 mg of AMRIX taken orally once daily, cyclobenzaprine immediate-release (IR) 10 mg three times a day, or placebo for 14 days.

The most common adverse reactions (incidence ≥3% in any treatment group and greater than placebo) were dry mouth, dizziness, fatigue, constipation, nausea, dyspepsia, and somnolence (see Table 1).

Table 1: Incidence of the Most Common Adverse Reactions Occurring in ≥ 3% of Patients in any Treatment Group* and Greater Than Placebo in the Two Phase 3, Double-Blind AMRIX Trials

	Placebo	AMRIX 15 mg	AMRIX 30 mg
	N=128	N=127	N=126
Dry mouth	2%	6%	14%
Dizziness	2%	3%	6%
Fatigue	2%	3%	3%
Constipation	0%	1%	3%
Somnolence	0%	1%	2%
Nausea	1%	3%	3%
Dyspepsia	1%	0%	4%

*AMRIX 15 mg QD, AMRIX 30 mg QD, or cyclobenzaprine IR tablets TID

AMRIX® (cyclobenzaprine hydrochloride extended-release capsules)

6.2 Postmarketing Experience

The following adverse reactions have been reported in clinical studies or postmarketing experience with AMRIX, cyclobenzaprine IR, or tricyclic drugs. Because some of these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In a postmarketing surveillance program of cyclobenzaprine IR, the adverse reactions reported most frequently were drowsiness, dry mouth, and dizziness and adverse reactions reported in 1% to 3% of the patients were: fatigue/tiredness, asthenia, nausea, constipation, dyspepsia, unpleasant taste, blurred vision, headache, nervousness, and confusion.

The following adverse reactions have been reported in postmarketing experience (AMRIX or cyclobenzaprine IR), in clinical studies of cyclobenzaprine IR (incidence <1%), or in postmarketing experience with other tricyclic drugs:

Body as a Whole: Syncope; malaise; chest pain; edema.

Cardiovascular: Tachycardia; arrhythmia; vasodilatation; palpitation; hypotension; hypertension; myocardial infarction; heart block; stroke.

Digestive: Vomiting; anorexia; diarrhea; gastrointestinal pain; gastritis; thirst; flatulence; edema of the tongue; abnormal liver function and rare reports of hepatitis, jaundice, and cholestasis; paralytic ileus, tongue discoloration; stomatitis; parotid swelling.

Endocrine: Inappropriate ADH syndrome.

Hematologic and Lymphatic: Purpura; bone marrow depression; leukopenia; eosinophilia; thrombocytopenia.

Hypersensitivity: Anaphylaxis; angioedema; pruritus; facial edema; urticaria; rash.

Metabolic, Nutritional, and Immune: Elevation and lowering of blood sugar levels; weight gain or loss.

Musculoskeletal: Local weakness; myalgia.

Nervous System and Psychiatric: Seizures, ataxia; vertigo; dysarthria; tremors; hypertonia; convulsions; muscle twitching; disorientation; insomnia; depressed mood; abnormal sensations; anxiety; agitation; psychosis, abnormal thinking and dreaming; hallucinations; excitement; paresthesia; diplopia; serotonin syndrome; neuroleptic malignant syndrome; decreased or increased libido; abnormal gait; delusions; aggressive behavior; paranoia; peripheral neuropathy; Bell's palsy; alteration in EEG patterns; extrapyramidal symptoms.

Respiratory: Dyspnea.

Skin: Sweating; photosensitization; alopecia.

Special Senses: Ageusia; tinnitus.

Urogenital: Urinary frequency and/or retention; impaired urination; dilatation of urinary tract; impotence; testicular swelling; gynecomastia; breast enlargement; galactorrhea.

7 DRUG INTERACTIONS

Based on its structural similarity to tricyclic antidepressants, AMRIX may have life-threatening interactions with MAO inhibitors *[see Contraindications (4)]*, may enhance the effects of alcohol, barbiturates, and other CNS depressants, may enhance the seizure risk in patients taking tramadol, or may block the antihypertensive action of guanethidine and similarly acting compounds.

Postmarketing cases of serotonin syndrome have been reported during combined use of cyclobenzaprine and other drugs, such as SSRIs, SNRIs, TCAs, tramadol, bupropion, meperidine, verapamil, or MAO inhibitors *[see Warnings and Precautions (5.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from case reports with AMRIX use in pregnancy have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In rats, decreased pup body weight and survival was noted at cyclobenzaprine doses ≥10 mg/kg/day (approximately ≥3 times the maximum recommended human dose (MRHD) of 30 mg/day), when administered orally during pregnancy and lactation *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

No adverse embryofetal effects were reported following oral administration of cyclobenzaprine during organogenesis to mice and rabbits at maternal doses up to 20 mg/kg/day (approximately 3 and 15 times the MRHD, respectively, on a mg/m^2 basis). Maternal toxicity characterized by decreased body weight gain was observed only in mice at the highest tested dose of 20 mg/kg/day.

Decreased pup body weight and survival were reported in a prenatal and postnatal study where pregnant rats were treated orally with cyclobenzaprine during pregnancy and lactation with maternal doses of 10 and 20 mg/kg/day (approximately 3 and 6 times the MRHD on a mg/m^2 basis). Maternal toxicity, characterized by a decreased body weight gain, was observed only at the highest tested dose of 20 mg/kg/day.

8.2 Lactation

Risk Summary

There are no data on the presence of cyclobenzaprine in either human or animal milk, the effects on a breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AMRIX and any potential adverse effects on the breastfed child from AMRIX or from the underlying maternal condition.

8.4 Pediatric Use
Safety and effectiveness of AMRIX have not been studied in pediatric patients.

8.5 Geriatric Use
Clinical studies of AMRIX did not include sufficient numbers of patients aged 65 and over to determine the safety and efficacy of AMRIX in the elderly population. The plasma concentration and half-life of cyclobenzaprine are substantially increased in the elderly when compared to the general patient population. Accordingly, use of AMRIX is not recommended in the elderly *[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment
The use of AMRIX is not recommended in patients with mild, moderate, or severe hepatic impairment *[see Warnings and Precautions (5.4) and Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

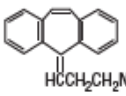
9.3 Dependence
Pharmacologic similarities among the tricyclic drugs require that certain withdrawal symptoms be considered when AMRIX is administered, even though they have not been reported to occur with this drug. Abrupt cessation of treatment after prolonged administration rarely may produce nausea, headache, and malaise. These are not indicative of addiction.

10 OVERDOSAGE

10.1 Manifestations
Although rare, deaths may occur from overdosage with AMRIX. Multiple drug ingestion (including alcohol) is common in deliberate cyclobenzaprine overdose. As management of overdose is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment.
Signs and symptoms of toxicity may develop rapidly after cyclobenzaprine overdose; therefore, hospital monitoring is required as soon as possible.
The most common effects associated with cyclobenzaprine overdose are drowsiness and tachycardia. Less frequent manifestations include tremor, agitation, coma, ataxia, hypertension, slurred speech, confusion, dizziness, nausea, vomiting, and hallucinations. Rare but potentially critical manifestations of overdose are cardiac arrest, chest pain, cardiac dysrhythmias, severe hypotension, seizures, and neuroleptic malignant syndrome. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of cyclobenzaprine toxicity. Other potential effects of overdosage include any of the symptoms listed under *Adverse Reactions (6)*.

10.2 Management
General
As management of overdose is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment.
In order to protect against the rare but potentially critical manifestations described above, obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line, and initiate gastric decontamination. Observation with cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is necessary. If signs of toxicity occur at any time during this period, extended monitoring is required. Monitoring of plasma drug levels should not guide management of the patient. Dialysis is probably of no value because of low plasma concentrations of the drug.
Gastrointestinal Decontamination
All patients suspected of an overdose with AMRIX should receive gastrointestinal decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage and emesis is contraindicated.
Cardiovascular
A maximal limb-lead QRS duration of 0.10 seconds may be the best indication of the severity of the overdose. Serum alkalinization, to a pH of 7.45 to 7.55, using intravenous sodium bicarbonate and hyperventilation (as needed), should be instituted for patients with dysrhythmias and/or QRS widening. A pH >7.60 or a pCO_2 <20 mmHg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium, or phenytoin. Type 1A and 1C antiarrhythmics are generally contraindicated (e.g., quinidine, disopyramide, and procainamide).
CNS
In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines or, if these are ineffective, other anticonvulsants (e.g., phenobarbital, phenytoin). Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies, and then only in close consultation with a poison control center.
Psychiatric Follow-Up
Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Psychiatric referral may be appropriate.
Pediatric Management
The principles of management of child and adult overdosage are similar. It is strongly recommended that the physician contact the local poison control center for specific pediatric treatment.

11 DESCRIPTION
AMRIX is a skeletal muscle relaxant which relieves muscle spasm of local origin without interfering with muscle function. The active ingredient in AMRIX extended-release capsules is cyclobenzaprine hydrochloride, USP. Cyclobenzaprine hydrochloride (HCl) is a white, crystalline tricyclic amine salt with the empirical formula $C_{20}H_{21}N \cdot HCl$ and a molecular weight of 311.9. It has a melting point of 217°C, and a pK_a of 8.47 at 25°C. It is freely soluble in water and alcohol, sparingly soluble in isopropanol, and insoluble in hydrocarbon solvents. If aqueous solutions are made alkaline, the free base separates. Cyclobenzaprine HCl is designated chemically as 3-(*5H*-dibenzo[*a,d*] cyclohepten-5-ylidene)-*N,N*-dimethyl-1-propanamine hydrochloride, and has the following structural formula:



AMRIX extended-release capsules for oral administration are supplied in 15 and 30 mg strengths. AMRIX capsules contain the following inactive ingredients: diethyl phthalate NF, ethylcellulose NF (Ethocel Standard 10 Premium), gelatin, Opadry® Clear Y8-1-7006, sugar spheres NF (20-25 mesh), and titanium dioxide. AMRIX 15 mg capsules also contain D&C yellow #10, FD&C green #3, and FD&C red #40. AMRIX 30 mg capsules also contain FD&C blue #1, FD&C blue #2, FD&C red #40, and FD&C yellow #6.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Cyclobenzaprine relieves skeletal muscle spasm of local origin without interfering with muscle function. Cyclobenzaprine has not been shown to be effective in muscle spasm due to central nervous system disease. In animal models, cyclobenzaprine reduced or abolished skeletal muscle hyperactivity. Animal studies indicate that cyclobenzaprine does not act at the neuromuscular junction or directly on skeletal muscle. Such studies show that cyclobenzaprine acts primarily within the central nervous system at the brain stem as opposed to the spinal cord level, although an overlapping action on the latter may contribute to its overall skeletal muscle relaxant activity. Evidence suggests that the net effect of cyclobenzaprine is a reduction of tonic somatic motor activity, influencing both gamma (γ) and alpha (α) motor systems. Pharmacological studies in animals demonstrated a similarity between the effects of cyclobenzaprine and the structurally related tricyclic antidepressants, including reserpine antagonism, norepinephrine potentiation, potent peripheral and central anticholinergic effects, and sedation. Cyclobenzaprine caused slight to moderate increase in heart rate in animals.

12.3 Pharmacokinetics
Absorption
Following single-dose administration of AMRIX 15 mg and 30 mg in healthy adult subjects (n=15), C_{max}, AUC_{0-168h} and $AUC_{0-\infty}$ increased in an approximately dose-proportional manner from 15 mg to 30 mg. The time to peak plasma cyclobenzaprine concentration (T_{max}) was 7 to 8 hours for both doses of AMRIX.
A food effect study conducted in healthy adult subjects (n=15) utilizing a single dose of AMRIX 30 mg demonstrated a statistically significant increase in bioavailability when AMRIX 30 mg was given with food relative to the fasted state. There was a 35% increase in peak plasma cyclobenzaprine concentration (C_{max}) and a 20% increase in exposure (AUC_{0-168h} and $AUC_{0-\infty}$) in the presence of food. No effect, however, was noted in T_{max} or the shape of the mean plasma cyclobenzaprine concentration versus time profile. Cyclobenzaprine in plasma was first detectable in both the fed and fasted states at 1.5 hours.
When the contents of AMRIX capsules were administered by sprinkling on applesauce, it was found to be bioequivalent to the same dose when administered as an intact capsule.
In a multiple-dose study utilizing AMRIX 30 mg administered once daily for 7 days in a group of healthy adult subjects (n=35), a 2.5-fold accumulation of plasma cyclobenzaprine levels was noted at steady-state.
Metabolism and Excretion
Cyclobenzaprine is extensively metabolized and is excreted primarily as glucuronides via the kidney. Cytochromes P-450 3A4, 1A2, and, to a lesser extent, 2D6, mediate N-demethylation, one of the oxidative pathways for cyclobenzaprine. Cyclobenzaprine has an elimination half-life of 32 hours (range 8-37 hours; n=18); plasma clearance is 0.7 L/min following single-dose administration of AMRIX.
Special Populations
Elderly
Although there were no notable differences in C_{max} or T_{max}, cyclobenzaprine plasma AUC is increased by 40% and the plasma half-life of cyclobenzaprine is prolonged in elderly subjects greater than 65 years of age (50 hours) after dosing with AMRIX compared to younger subjects 18 to 45 years of age (32 hours). Pharmacokinetic characteristics of cyclobenzaprine following multiple-dose administration of AMRIX in the elderly were not evaluated.
Hepatic Impairment
In a pharmacokinetic study of immediate-release cyclobenzaprine in 16 subjects with hepatic impairment (15 mild, 1 moderate per Child-Pugh score), both AUC and C_{max} were approximately double the values seen in the healthy control group. The pharmacokinetics of cyclobenzaprine in subjects with severe hepatic impairment is not known.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
Long-term studies were conducted in CD-1 mice and Sprague-Dawley rats with oral cyclobenzaprine to evaluate its carcinogenic potential. In an 81-week carcinogenicity study, metastatic hemangiosarcoma was seen in 3 of 21 male mice at 10 mg/kg/day (approximately 2 times the maximum recommended human dose (MRHD) of 30 mg/day

on a mg/m² basis). In a 105-week carcinogenicity study, malignant astrocytoma was seen in 3 of 50 male rats at 10 mg/kg/day (approximately 3 times the MRHD on a mg/m² basis). There were no tumor findings in female mice or rats.

Mutagenesis

Cyclobenzaprine HCl was not mutagenic or clastogenic in the following assays: an *in vitro* Ames bacterial mutation assay, *in vitro* Chinese hamster ovary (CHO) cell chromosomal aberration test, and *in vivo* mouse bone marrow micronucleus assay.

Impairment of Fertility

Cyclobenzaprine HCl, when administered 70 and 14 days prior to mating to male and female rats, respectively, had no effects on fertility or reproductive performance at oral doses up to 20 mg/kg/day (approximately 6.5 times the MRHD on a mg/m² basis).

13.2 Animal Toxicology and/or Pharmacology

In a 67-week study with rats that received cyclobenzaprine at oral doses of 10, 20, or 40 mg/kg/day (3 to 15 times the MRHD on mg/m² basis), there were findings in the liver consisting of midzonal vacuolation with lipidosis for males and midzonal and centrilobular hepatocytic enlargement for females. In addition, there were findings of centrilobular coagulative necrosis. In the higher dose groups, these microscopic changes were seen after 26 weeks and even earlier in rats that died prior to 26 weeks; at lower doses, these changes were not seen until after 26 weeks.

In a 26-week study with Cynomolgus monkeys that received cyclobenzaprine at oral of doses of 2.5, 5, 10, or 20 mg/kg/day, one monkey at 20 mg/kg/day (15 times the MRHD on mg/m² basis) was euthanized in week 17. Morbidity for this animal was attributed to findings of chronic pancreatitis, cholecystitis, cholangitis, and focal liver necrosis.

14 CLINICAL STUDIES

Efficacy was assessed in two double-blind, parallel-group, active-controlled, placebo-controlled studies of identical design of AMRIX 15 mg and 30 mg taken once daily, between 6:00 and 7:00 PM, cyclobenzaprine 10 mg three times a day, or placebo for 14 days in patients with muscle spasms associated with acute painful musculoskeletal conditions.

There were significant differences in the primary efficacy analysis, the patient's rating of medication helpfulness, between the AMRIX 15 mg group and the placebo group at Days 4 and 14 in one study and between the AMRIX 30 mg group and the placebo group at Day 4 in the second study.

Table 2: Patients' Rating of Medication Helpfulness - Study 1*

	Day 4		Day 14	
	Number of Patients (%)		Number of Patients (%)	
	Placebo (N = 64)	AMRIX 30 mg (N = 64)	Placebo (N = 64)	AMRIX 30 mg (N = 64)
Excellent	1 (2%)	3 (5%)	12 (19%)	15 (23½)
Very Good	5 (8%)	13 (20%)	9 (14%)	19 (30½)
Good	15 (23½)	22 (34%)	10 (16%)	15 (23½)
Fair	24 (38½)	20 (31%)	16 (25%)	10 (16½)
Poor	10 (16½)	5 (8%)	9 (14%)	4 (6%)
Missing	9 (14%)	1 (2%)	8 (13%)	1 (2%)

*Percentages are rounded to the nearest whole percent.

Table 3: Patients' Rating of Medication Helpfulness - Study 2*

	Day 4		Day 14	
	Number of Patients (%)		Number of Patients (%)	
	Placebo (N = 64)	AMRIX 15 mg (N = 63)	Placebo (N = 64)	AMRIX 15 mg (N = 63)
Excellent	1 (2%)	2 (3%)	10 (16%)	13 (21½)
Very Good	10 (16½)	12 (19%)	12 (19%)	21 (33½)
Good	14 (22½)	21 (33%)	13 (20%)	9 (14%)
Fair	16 (25½)	17 (27%)	14 (22%)	10 (16½)
Poor	19 (30½)	6 (10½)	12 (19%)	5 (8%)
Missing	4 (6%)	5 (8%)	3 (5½)	5 (8%)

*Percentages are rounded to the nearest whole percent.

In addition, one of the two studies demonstrated significant differences between the AMRIX 30 mg group and the placebo group in terms of patient-rated relief from local pain due to muscle spasm at Day 4 and Day 8, in patient-rated restriction of movement at Day 4 and Day 8, and in patient-rated global impression of change at Day 4, Day 8, and Day 14.

In both studies, there were no significant treatment differences between the AMRIX treatment groups and the placebo group in physician's global assessment, patient-rated restriction in activities of daily living, or quality of nighttime sleep.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

AMRIX extended-release capsules are available in 15 and 30 mg strengths, packaged in bottles of 60 capsules. AMRIX 15 mg capsules (NDC 63459-700-60) are orange/orange and are embossed in blue ink with "15 mg" on the body, and Cephalon "C" logo, "Cephalon", and a dashed band on the cap. AMRIX 30 mg capsules (NDC 63459-701-60) are blue/red and are embossed in white ink with "30 mg" on the body, and Cephalon "C" logo, "Cephalon", and a dashed band on the cap.

AMRIX® (cyclobenzaprine hydrochloride extended-release capsules)

16.2 Storage and Handling

Dispense in a tight, light-resistant container as defined in the USP/NF.

Store at 25°C (77°F); excursions permitted to 15 - 30°C (59 - 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

- Instruct patients to swallow AMRIX capsules intact or to sprinkle capsule contents on a tablespoon of applesauce and swallow immediately without chewing.
- Advise patients to stop taking AMRIX and to notify their physician right away if they experience symptoms of an allergic reaction, such as difficulty breathing, hives, swelling of face or tongue, or itching.
- Advise patients that AMRIX should not be taken with MAO inhibitors or within 14 days after their discontinuation.
- Caution patients about the risk of serotonin syndrome with concomitant use of AMRIX and other drugs, such as SSRIs, SNRIs, TCAs, tramadol, bupropion, meperidine, verapamil, or MAO inhibitors. Advise patients of the signs and symptoms of serotonin syndrome *[see Warnings and Precautions (5.1)]* and instruct patients to seek medical care immediately if they experience these symptoms.
- Advise patients to stop taking AMRIX and to notify their physician right away if they experience arrhythmias or tachycardia.
- Advise patients that AMRIX may enhance the impairment effects of alcohol. These effects may also be seen if AMRIX is taken with other CNS depressants.
- Caution patients about operating an automobile or other hazardous machinery until it is reasonably certain that AMRIX therapy will not adversely affect their ability to engage in such activities.
- Advise patients to take AMRIX at approximately the same time each day.

teva

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Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454

Manufactured By:
Adare Pharmaceuticals, Inc.
Vandalia, OH 45377

AMR-010

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US Patent Nos. 7387793, 7544372, 7790199, 7820203, 7829121, 9375410, 9399025

PATIENT INFORMATION

AMRIX® (am-rix)
(cyclobenzaprine hydrochloride extended-release capsules)

What is AMRIX?

AMRIX is a prescription medicine used along with rest and physical therapy to help treat muscle spasm due to acute, painful musculoskeletal problems.

AMRIX should only be used for up to 2 or 3 weeks. It is not known if AMRIX is effective when used for longer periods.

It is not known if AMRIX is safe and effective in children.

Do not take AMRIX if you:

- are allergic to cyclobenzaprine or any of the ingredients in AMRIX. See the end of this Patient Information leaflet for a complete list of ingredients in AMRIX.
  Talk to your healthcare provider or get medical help right away if you have symptoms of an allergic reaction such as:
  - difficulty breathing
  - hives
  - swelling of your face or tongue
  - itching
- are taking certain antidepressants, known as monoamine oxidase (MAO) inhibitors or it has been 14 days or less since you stopped taking a MAO inhibitor. Ask your healthcare provider or pharmacist for a list of these medicines if you are not sure.
- have had a recent heart attack
- have heart rhythm problems (arrhythmias)

continued

- have heart failure
- have an overactive thyroid (hyperthyroidism)

Talk to your healthcare provider before taking this medicine if you have any of the conditions listed above.

Before taking AMRIX, tell your healthcare provider about all of your medical conditions, including if you:

- have a history of eye problems including glaucoma
- have heart problems or have had a heart attack
- have liver problems
- have trouble emptying your bladder (urinary retention)
- are pregnant or plan to become pregnant. It is not known if AMRIX will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if AMRIX passes into your breast milk. Talk to your healthcare provider about the best way to best way to feed your baby if you take AMRIX.

Tell your healthcare provider about all the medicines you take including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Especially tell your healthcare provider if you take:

- a medicine to treat depression, mood, anxiety, psychotic, or thought disorders
- a pain medicine called tramadol or meperidine
- barbiturates or other medicines that depress your central nervous system (CNS depressants)
- a medicine that prevents nerve impulses (anticholinergic medicines)
- a medicine to help quit smoking called bupropion
- a blood pressure medicine called verapamil

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider or pharmacist when you get a new medicine.

How should I take AMRIX?

- Take AMRIX exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much AMRIX to take and when to take it.
- Your healthcare provider may change your AMRIX dose if needed.
- Take AMRIX around the same time every day.
- Swallow AMRIX capsules whole.
- If you have difficulty swallowing AMRIX capsules, tell your healthcare provider. Your healthcare provider may recommend opening the AMRIX capsule and mixing the contents with applesauce.
- AMRIX should only be taken for short periods (up to two or three weeks).
- If you take too much AMRIX, call your healthcare provider or go to the nearest hospital emergency room right away.

What should I avoid while taking AMRIX?

You should not drink alcohol until you know how AMRIX affects you. Taking AMRIX with alcohol or other medicines that depress your central nervous system can slow your thinking and physical response times.

Do not drive, operate machinery, or do other dangerous activities until you know how AMRIX affects you.

What are the possible side effects of AMRIX?

AMRIX may cause serious side effects, including:

- **Serotonin syndrome** is a serious medical condition that may happen when AMRIX is taken with certain other medicines. Call your healthcare provider right away or go to the nearest hospital emergency room if you have some or all of these symptoms suggestive of serotonin syndrome:
  - agitation, hallucinations, coma, or other changes in mental status
  - coordination problems or muscle twitching (overactive reflexes)
  - fast heartbeat, high or low blood pressure
  - sweating or fever
  - nausea, vomiting, or diarrhea
  - muscle stiffness or tightness

continued

AMRIX® (cyclobenzaprine hydrochloride extended-release capsules)

- **AMRIX may cause serious side effects that may lead to heart attack or stroke.** Call your healthcare provider right away or go to the nearest hospital emergency room if you have:
  - irregular or abnormal heartbeats (arrhythmias)
  - fast heartbeat (tachycardia)

The most common side effects of AMRIX include:

- dry mouth
- dizziness
- fatigue
- constipation
- nausea
- upset stomach
- drowsiness

These are not all the possible side effects of AMRIX.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store AMRIX?

- Store AMRIX at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep AMRIX in a tightly closed container, and keep AMRIX out of light.
- **Keep AMRIX and all medicines out of the reach of children.**

General information about the safe and effective use of AMRIX.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use AMRIX for a condition for which it was not prescribed. Do not give AMRIX to other people, even if they have the same symptoms you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about AMRIX that is written for healthcare professionals.

What are the ingredients in AMRIX?

Active Ingredient: cyclobenzaprine hydrochloride USP

Inactive Ingredients: diethyl phthalate NF, ethylcellulose NF (Ethocel Standard 10 Premium), gelatin, Opadry® Clear YS-1-7006, sugar spheres NF (20-25 mesh), and titanium dioxide.

AMRIX 15 mg capsules also contain: D&C yellow #10, FD&C green #3, and FD&C red #40.

AMRIX 30 mg capsules also contain: FD&C blue #1, FD&C blue #2, FD&C red #40, and FD&C yellow #6.

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Vandalia, OH 45377

AMRPL-005

For more information, go to www.AMRIX.com or call 1-888-483-8279.

This Patient Information has been approved by the U.S. Food and Drug Administration Revised: April 2019