PROTOCOL

TONIX
PHARMACEUTICALS

TNX-OX-CM201

A **P**hase 2, Double-blind, **R**andomized, Multicenter, Plac**E**bo-controlled, Three Arm Parallel Study to E**V**aluate the **E**fficacy a**N**d Safety of **T**NX-1900 (**I**ntranasal **O**xytocin) in Patients with Chro**N**ic Migraine

["PREVENTION" Study]

Amendment 4, Release Date: 11 January 2023
Replaces Amendment 3, Release Date: 22 September 2022
Replaces Amendment 2, Release Date: 21 June 2022
Replaces Amendment 1, Release Date: 10 September 2021
Original Protocol, Release Date: 13 August 2021

Sponsor: Tonix Pharmaceuticals, Inc.
26 Main Street, Suite 101
Chatham, NJ 07928

[redacted]

INVESTIGATOR'S AGREEMENT

I have read the TNX-OX-CM201 protocol entitled "A Phase 2, Double-blind, Randomized, Multicenter, Placebo-controlled, Three Arm Parallel Study to Evaluate the Efficacy and Safety of TNX-1900 (Intranasal Oxytocin) in Patients with Chronic Migraine, Amendment 03" and agree to conduct the study as outlined. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

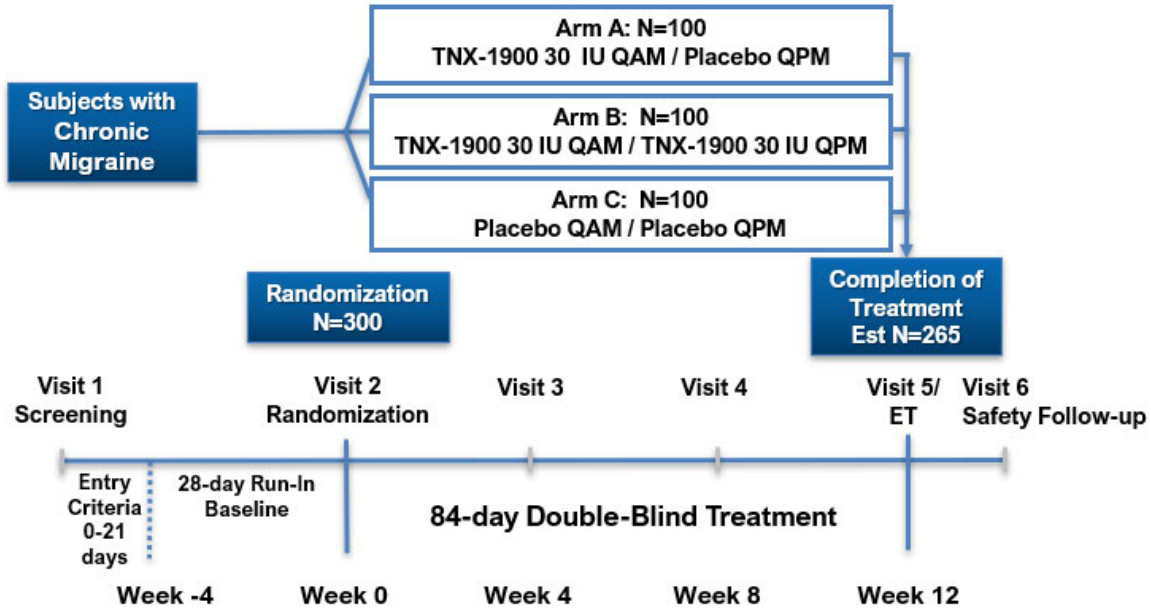
PROCEDURES IN CASE OF EMERGENCY

Emergency Contact Information

SYNOPSIS

Title	A Phase 2, Double-blind, Randomized, Multicenter, Placebo-controlled, Three Arm Parallel Study to Evaluate the Efficacy and Safety of TNX-1900 (Intranasal Oxytocin) in Patients with Chronic Migraine
Protocol Number:	TNX-OX-CM201
Name of Sponsor:	Tonix Pharmaceuticals, Inc
Phase of Development:	Phase 2
Name of Investigational Product:	TNX-1900
Name of Active Ingredient:	Oxytocin
Therapeutic Area:	Chronic Migraine
Study Objectives	
Objectives:	• Evaluate the efficacy of 2 TNX-1900 treatment regimens at 30 International Units (IU) once daily (QD) and 30 IU twice daily (BID) compared to placebo in chronic migraineurs. • Evaluate the safety and tolerability of 2 TNX-1900 treatment regimens at 30 IU QD and 30 IU BID compared to placebo in chronic migraineurs.
Study Design	
Description:	This is a double-blind, randomized, placebo-controlled, multicenter, 3 arm parallel Phase 2 study. Men and women with a current diagnosis of chronic migraine (CM) according to the International Headache Society (IHS) International Classification of Headache Disorders, 3rd edition (ICHD-3) and who meet the criteria for the study during Screening will enter a Run--in Period in which each patient's migraine/headache activity will be recorded for at least 28 days. At the end of the Run-in Period, eligible patients will be randomized at a 1:1:1 ratio to one of the 3 treatment arms: TNX-1900 at a fixed daily dose of 30 IU QD (Treatment Arm A), a fixed daily dose of 30 IU BID (Treatment Arm B) or placebo (Treatment Arm C) for the duration of a 12-week Treatment Period. Randomization will be stratified by study site and preventive migraine medication (use of a single preventive vs. no preventive). All patients will administer study drug twice a day, mornings and evenings, in a double-blind design. <u>Screening/Washout/Run-In (V1: Screening Visit)</u> After providing written informed consent, patients will be assessed for eligibility (including medical history, migraine headache history, medication use, physical exam, nasal exam, vital signs, clinical labs, and electrocardiogram [ECG]). Eligible patients will be trained on the e-diary during the Screening Visit and will enter a 28-day Run-In period which will last for at least 28 days. Patients who need to wash out excluded medications will have up to an additional 21

	days in the Run-In period, but every effort should be made to minimize to the fewest days needed for the given washout period(s) in the protocol. During the Run-In, patients will be required to answer questions daily regarding headaches and rescue (abortive) medication use on an electronic diary (e-diary) regardless of whether patients experienced a headache on that day. It is a patient's responsibility to be compliant with e-diary entries. Each patient's headache frequency, as well as e-diary compliance, will be evaluated at the end of the Run-in Period to ensure a patient meets all required eligibility criteria for treatment randomization. For evaluating randomization eligibility, the last 28 days of Run-In diary entries will be used, which includes diary entries logged on the morning of the Baseline Visit. A patient **must not** be informed of the minimum number of headache days and migraine headache days required to be randomized to study treatment as this might bias e-diary entries during Run-in Period. During this Screening and Run-In Period, if any test results come back and indicate a patient's ineligibility for the study, the patient should be considered a screen-failure (SF) and informed that they are not eligible for the study and can stop completing the e-diary. However, if the investigator determines that the patient should be brought back into the clinic for re-testing, the patient should continue completing the e-diary until a final determination regarding eligibility is made. In addition, any patients not meeting the randomization criteria will be considered a failure. <u>Double-blind Treatment Period (V2: Baseline/Randomization Visit; and V3, 4, 5: Treatment Visits)</u> The Treatment Period will last for about 84 days. At Visit 2, eligible patients will be randomized 1:1:1 to one of 3 treatment arms (A, B or C) as summarized above. Randomization will be stratified by study site and concomitant migraine preventative medication (use of a single preventative vs no preventative). Patients will be required to answer daily questions regarding headaches, rescue (abortive) medication use, and study drug compliance using an e-diary, regardless of whether a headache occurred that day. All patients who withdraw early from the study will be encouraged to complete the Early Termination Visit for safety evaluations (Visit 5 [V5]) within 7 days from withdrawal, followed by the Safety Follow-up Visit (Visit 6) approximately 14 days from the last study drug administration. <u>Safety Follow-up Period (Visit 6: in-person Safety Follow-up Visit)</u> Approximately 14 days (+4 days window) after Visit 5 or End of Treatment (ET) Visit, all randomized patients will attend a Safety Follow-up Visit.



Dose and Route of Administration:

Investigational Product (TNX-1900)

TNX-1900 is provided as a preservative-free, aqueous, oxytocin containing solution for intranasal delivery. TNX-1900 will be supplied as a 150 IU/mL concentration of oxytocin. One dose of study drug requires 2 administration sprays into the nostrils (1 spray per nostril). The volume of each spray is 0.10 mL. Given the 150 IU/mL concentration, each spray delivers 15 IU of study drug. Consequently, one dose (2 sprays: one spray per nostril) equates to a 30 IU oxytocin total dose.

Dose	Treatment	Administration
30 IU QAM / Placebo QPM	A	1 dose from 'MORNING' nasal spray bottle = 1 spray each nostril of TNX-1900 (2 sprays total) 1 dose from 'EVENING' nasal spray bottle = 1 spray each nostril of placebo (2 sprays total)
30 IU QAM / 30 IU QPM	B	1 dose from 'MORNING' nasal spray bottle = 1 spray each nostril of TNX-1900 (2 sprays total) 1 dose from 'EVENING' nasal spray bottle = 1 spray each nostril of TNX-1900 (2 sprays total)
Placebo QAM / Placebo QPM	C	1 dose from 'MORNING' nasal spray bottle = 1 spray each nostril of placebo (2 sprays total) 1 dose from 'EVENING' nasal spray bottle = 1 spray each nostril of placebo (2 sprays total)

The nasal spray bottle of MORNING study drug will be clearly labeled 'MORNING'. The EVENING study drug will be clearly labeled 'EVENING'.

During the double-blind Treatment Period, patients will be instructed to self-administer ONE dose (2 sprays total, 1 spray per nostril) of 'MORNING' study drug daily at a fixed time in the morning and ONE dose (2 sprays total, 1 spray per nostril) of 'EVENING' study drug at a fixed time in the evening.

	Each patient will be dispensed 2 bottles at each applicable visit. Study drug will be self-administered. Patients will be trained in the use of the nasal applicator prior to home use and will receive an Instructions for Use document. Priming of each dispensed bottle should be conducted by site staff at V2, V3, and V4. Prior to leaving the clinic at Baseline/Randomization/Visit 2, the patient will take their first dose from the Morning dose bottle regardless of time of day. Also, on the night of Visit 2, patients should administer from the Evening dose bottle the same evening at home, with a minimum period between the two doses of at least 6 hours. At subsequent visits (V3, V4, V5), the patient should take their AM dose of study drug from their existing study drug bottle, prior to the site collecting it and dispensing new study drug bottles. Patients should be reminded to take the AM dose prior to arriving at the clinic if possible. **Reference Therapy (Placebo)** Placebo is provided as a preservative-free, colorless aqueous solution containing the same excipients as TNX-1900. Placebo does not contain oxytocin. Administration instructions are identical to those for TNX-1900.
Duration of Study Participation:	Approximately 18-21 weeks including a 14-day Safety Follow-up Period
Study Sites:	Approximately 25 study centers in the United States
Study Population:	Adult migraineurs with chronic migraine as defined by ICHD-3. Potential patients must have met criteria for chronic migraine for greater than 3 months prior to study entry, and onset of migraine episodes must be prior to the age of 50 years with a history of migraine for at least one year prior to study entry.
Sample Size Calculation and Power Consideration:	The planned total number of randomized patients is approximately 300 and will be randomized 1:1:1 to TNX-1900 30 IU QAM, placebo QPM: TNX-1900 30 IU BID: or placebo BID. [redacted]

	[redacted]
Eligibility Criteria	
Inclusion Criteria:	1. Men and women aged 18 to 65 years, inclusive, at the time of Visit 1. 2. History of migraine with or without aura (Appendix A) for at least 1 year and onset at < 50 years of age. Patient must also have a history of chronic migraine > 3 months prior to Visit 1 as defined by IHS ICHD-3 (Appendix A) 3. Able to differentiate migraine or probable migraine headache from other headaches. 4. Patients can be on stable ≤ 1 preventive medication and any number of abortive migraine medications for 90 days prior to Screening and during the study. All treatments, other than the study drug, thought to have preventive efficacy in migraine should not be started or discontinued during the entire study period. *Note: Up to approximately 30% of the patients randomized into the study can be on 1 preventative medication. Once this category is filled, only patients who are not on any preventative medications can be randomized into the study. From study start, sites should enroll patients into both categories in parallel until informed otherwise.* 5. If female, is either not of childbearing potential (defined as postmenopausal for at least 1 year or surgically sterile [e.g., 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. Bilateral tubal ligation d. Double-barrier method (condoms, sponge, diaphragm, or vaginal ring with spermicidal jelly or cream). e. Partners of vasectomized (> 1 year ago) males in monogamous relationships. f. Females involved only in same sex relationships. g. Females practicing abstinence may have the birth control requirement waived only with Medical Monitor approval. 6. If male, is either vasectomized (> 1 year ago) or will be practicing one of the following methods of birth control throughout the study: a. Partner in monogamous relationship with female practicing one of the methods in 5a or 5b above. b. Double-barrier method (condoms, sponge, diaphragm, or vaginal ring with spermicidal jelly or cream.). c. Males involved only in same sex relationships. d. Males practicing abstinence may have the birth control requirement waived only with Medical Monitor approval.

	7. The patient is willing and able to comply with all protocol-specified requirements. 8. Capable of reading and understanding English and able to provide written informed consent to participate.
Exclusion Criteria:	1. History of cluster headache. 2. Presence of headaches more than 26 days a month on average for the 6 months prior to Screening. 3. Failed to benefit from an adequate dose and duration, in the investigator's judgment (e.g., one month of β-blocker), of 3 or more migraine preventive medications. 4. History of seizure disorder other than childhood febrile seizures. 5. The patient is at increased risk of suicide based on the investigator's judgment, 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/or any suicidal behavior within the past 12 months). 6. In general, chronic use of systemic steroidal or non-steroidal anti-inflammatory drugs (NSAIDs) and combination products containing NSAIDs for any indication will be prohibited during the Screening Period and during the study. The following instructions should be followed: a. Excepting topical usage, chronic use of systemic steroidal anti-inflammatory drugs is not allowed for any indication. b. Chronic use of NSAIDs on a daily basis is not allowed; therefore, those on daily NSAIDs necessary for treatment of other medical conditions, e.g., arthritis, should not be enrolled; NSAIDs may be used as needed (PRN) for headache pain **only** if they are part of patient's typical migraine/headache abortive treatment regimen; other use of NSAIDs is allowed as needed for other acute pain syndromes, but daily use is not allowed. 7. Use of opiates or barbiturates more than 4 days per month for more than 3 consecutive months prior to Visit 1 and during the study. 8. Use of the following non-pharmacological treatments for headache or any other indication, is prohibited within 90 days prior to Screening and throughout the entire study: any electrical or magnetic stimulating devices (e.g., non-invasive vagal nerve stimulation [GammaCore], transcranial magnetic stimulation [TMS Mini], or Remote Electrical Neuromodulation [REN or Nerivio]). Any types of psychotherapy stress management, acupuncture, chiropractic manipulation, and physical therapy is prohibited within 90 days of Screening and throughout the entire study **only** if the treatment is specifically targeted for the relief of headaches, migraines, or any type of head and neck pain. Otherwise, such treatments must have been ongoing for at least 90 days prior to Visit 1 with a plan to continue throughout the study to be eligible. Also, occipital nerve blocks or botulinum toxin treatments for any indication are prohibited within 90 days of Screening and throughout the entire study.

	9. Use of over-the-counter (OTC) nasal products (i.e., saline spray, Neti-Pot, Naväge® etc.) during the study. 10. History of unstable psychiatric illness requiring hospitalization in the 12 months prior to Visit 1. Coexisting conditions, such as depression and anxiety, may be included if they are stable on current treatment regimens (with no change in treatment regimen for the last 90 days) and no planned changes during the study. 11. History of or evidence supporting 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) and/or the investigator's opinion. 12. Body mass index (BMI) > 40 kg/m^2. 13. Any clinically significant medical condition that, in the opinion of the investigator, would make the patient unsuitable for study participation and completion. 14. Any use of intranasal corticosteroid medications or conditions in which use of intranasal corticosteroids may be indicated during the study, e.g., unstable allergic rhinitis that has previously required intranasal corticosteroids. Intranasal corticosteroid use is not allowed within 28 days of Baseline/Randomization/Visit 2 and during the treatment phase or follow-up period of the study. 15. Clinically significant laboratory or ECG abnormality (in the investigator's opinion) based on Screening laboratory tests, or any of the following: a. Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 2 times the upper level of normal (ULN) b. Serum creatinine > 1.2 times the ULN c. Thyroid stimulating hormone (TSH) > 1.5 times the ULN d. HbA1c > 7.5% e. Resting heart rate ≤ 45 bpm or ≥ 100 bpm f. Clinically significant arrhythmia or heart block g. Corrected QT interval by the Fridericia formula (QTcF) > 470 ms for females; and > 450 ms for males. 16. History of chronic nasal obstruction or local pathology in nostril pathway which, in the opinion of the investigator, would prevent appropriate nasal administration of the study drug. 17. Known allergy or hypersensitivity to oxytocin containing products. 18. Positive results for illegal or abused substances other than cannabis/tetrahydrocannabinol at Screening or Baseline. 19. Women who are pregnant, planning to become pregnant, or nursing during the study. 20. Currently enrolled in or have participated within the last 30 days in a clinical trial involving an investigational product prior to Visit 1 (does not apply to anti-CGRP agent studies covered in Exclusion 21). 21. Patients who recently discontinued treatment with an anti-calcitonin-gene-related peptide (CGRP) antibody or participated in an anti-CGRP antibody clinical study must be at least 4 months from the last drug

	administration prior to Visit 1. Patients in an extended observational period from such an anti-CGRP antibody study and are at least 4 months from the last drug administration prior to Visit 1 are eligible. Small molecule anti-CGRP treatments, e.g., gepants, are treated similarly but only must be at least 1 month from last drug administration prior to Visit 1. 22. History of clinically significant and currently relevant cardiovascular disease or vascular ischemia (including myocardial, cerebral, peripheral extremity or other ischemic event) or thromboembolic events (arterial or venous thrombotic or embolic events) such as cerebrovascular accident, deep vein thrombosis, or pulmonary embolism. Recent myocardial infarction (within the last 2 years). Diagnosed with heart failure. 23. History of alcohol or drug abuse within the prior year, or alcohol or drug dependence within the prior 5 years, as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).
Eligibility Criteria for Randomization:	Up to approximately 30% of the patients randomized into the study can be on 1 migraine preventative medication. Once this category is filled, only patients who are not on any preventative medications can be randomized into the study. *From study start, sites should enroll patients into both categories in parallel until informed otherwise.* For a patient to be eligible for randomization, the following should be observed during the last 28 days of the Run-in Period: 1. Demonstrate an ability to properly use e-diary. 2. Complete ≥ 82% of the e-diary daily entries (at least 23 days out of the 28-day period). 3. At least 14 headache (migraine-like or tension-type-like) days 4. At least 8 days where the patient experiences any of the following: • An attack lasting 4 hours or more and meeting the ICHD-3 criteria (diagnostic criteria C and D) for migraine without aura (Appendix A) • Migraine with aura • Probable migraine (a migraine subtype fulfilling all but one criterion (B-D) for migraine without aura) • An attack of any duration that was believed by the patient to be a migraine and was relieved by a triptan, ergot derivative, or other migraine-specific abortive medication. It is important to note that the last 28 days of Run-In diary entries includes diary entries logged on morning of the Baseline Visit. Patients should be reminded to complete the required e-diary entries on the morning of the Baseline Visit. Patients may be withdrawn from the Run-in Period prior to the end of 28 days if patients are determined mathematically to be unable to meet the headache criteria required by the protocol.

	Those patients who only miss the e-diary compliance requirement (i.e., compliance less than 82%) and otherwise are qualified for randomization may be given the opportunity to either extend or repeat the Run-in Period. Any extension will be considered on a case-by-case basis and require medical monitor approval. At Baseline/Randomization/V2, patients must still meet all inclusion criteria and none of the exclusion criteria and be in good general health, or with only stable and non-serious conditions that, in the opinion of the investigator, will not place the patient at risk.
Primary Efficacy Endpoint:	Mean change in the number of monthly migraine headache days from the last 28 days of Baseline to the last 28 days of treatment (i.e., month 3). A migraine headache day is any calendar day (0:00 to 23:59) in which the patient records in the e-diary: • An attack lasting 4 hours or more and meeting the ICHD-3 criteria for migraine without aura (Appendix A), or • A migraine with aura, or • An attack that meets ICHD-3 criteria for probable migraine, (a migraine subtype fulfilling all but one criterion (B-D) for migraine without aura), or • An attack of any duration that was believed by the patient to be a migraine and was relieved by a triptan, ergot derivative, or other migraine-specific abortive medication.
Key Secondary Efficacy Endpoints	• Proportion of patients experiencing a ≥ 50% reduction in the number of migraine headache days from the last 28 days of Baseline to the last 28 days of treatment in each treatment group. • Mean change in the number of days using rescue medication (triptan, ergot derivative, or other migraine-specific acute medication) from the last 28 days of Baseline to the last 28 days of treatment. • Proportion of patients with a Patient Global Impression of Change (PGIC) rating of 1, "very much improved", or 2, "much improved", at Week 12. • Mean change in the number of moderate or severe headache days from the last 28 days of Baseline to the last 28 days of treatment. A moderate or severe headache day is defined as any calendar day wherein a patient records a headache or migraine of moderate or severe peak intensity in the e-diary. • Mean change in the number of migraine headache days from the last 28 days of Baseline to average number per 28 days over the entire 12-week duration of Treatment Period. • Mean change from Baseline in the Migraine-Specific Quality of Life Questionnaire (MSQ v2.1) at Week 12.

Efficacy Secondary Endpoints:	• Mean change from Baseline in the Migraine Disability Assessment (MIDAS) Test total score at Week 12. • Mean change from Baseline in the Hospital Anxiety and Depression Scale (HADS) total score at Week 12. • Mean change from Baseline in patient-rated Changes in Sexual Functioning Questionnaire Short-Form (CSFQ-14) total score in males and in females, analyzed separately, at Week 12.
Exploratory Endpoints:	• Proportion of patients experiencing a ≥ 75% reduction in the number of migraine headache days from the last 28 days of Baseline to the last 28 days of treatment in each treatment group. • Proportion of patients with fewer than 14 headache days or fewer than 8 migraine headache days per 4 weeks over the 12-week period. • Mean change from Baseline in number of headache free days from the last 28 days of Baseline to the last 28 days of treatment. • PGIC rating (1-7) at Week 12
Safety Endpoints:	• Change in suicidality using the C-SSRS scale • Incidence of adverse events (AEs) • Changes from Baseline in clinical laboratory tests • Changes from Baseline in vital signs • Change from Baseline in ECG parameters • Clinically significant change(s) in physical examination findings • Clinically significant change(s) in nasal examination findings • Changes from Baseline in the Hospital Anxiety and Depression Scale (HADS) total score at Week 12 • Changes from Baseline in patient-rated Changes in Sexual Functioning Questionnaire Short-Form (CSFQ-14) in males and in females, described separately
Statistical Methods:	The modified intention-to-treat population (mITT), defined as all randomized patients who receive at least 1 dose of study drug and have at least one post-Baseline, evaluable month (that is, at least one of the three 28-day periods has at least 14 non-missing e-diary entries), will be used as the primary population for all efficacy analyses. The sample size and power calculations for this study are based on the analysis of the primary efficacy outcome variable: mean change in the number of migraine headache days from the last 28 days of Baseline to the last 28 days of treatment in each treatment group. **<u>Efficacy Analysis</u>** The primary efficacy endpoint of change from Baseline will be analyzed using a mixed-effects model of repeated measures (MMRM) with fixed effects of treatment, month, baseline value, treatment by month interaction,

	baseline by month interaction, site, and stratification factor (preventive medication use); an unstructured covariance matrix will be used. Several secondary efficacy outcomes will be measured and compared between treatment groups. Appropriate methodology for multiplicity will be applied across doses and to the key secondary efficacy endpoints to maintain overall alpha of 0.05; this will be specified in the Statistical Analysis Plan (SAP). Formal safety data monitoring is not planned for this study. 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 end of the Treatment Period is above a pre-specified threshold; or to stop the study early for futility if the conditional power is sufficiently low. Full details of the interim analysis will be included in the SAP and finalized prior to execution of the interim analysis. **Safety Analysis** AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized overall and by preferred term and system organ class. AEs will also be summarized by severity and relationship to study drug. Serious AEs, AEs involving the nasal passages, and AEs leading to discontinuation of study drug will also be summarized. Actual values and changes from Baseline for clinical laboratory test results, ECG parameters, vital signs, HADS scores, and CSFQ-14 scores 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, based on the C-SSRS, will be summarized by treatment group.

SCHEDULE OF ASSESSMENTS

Study Phase	**Screening/Washout (Up to 21 days)** **Run-In (At least 28 days*)**	**Treatment 84 days**				**Follow-up[b] 14 days**
Study Visit	**V1 Screening**	**V2 Baseline/ Randomization**	**V3**	**V4**	**V5 Or Early Termination[a]**	**Visit 6 End-of-Study In-Person**
Study Week			**Week 4**	**Week 8**	**Week 12**	**Week 14**
Study Days	**Day** -49 to Day -1	**Day 1**	**Day 29 ± 4d**	**Day 57 ± 4d**	**Day 85 ± 4d**	**Day 99 ± 4d**
Informed Consent	X					
Inclusion/ Exclusion Criteria	X	X				
Demographics	X					
Medical and Medication History	X	X[c]				
Adverse Events Assessment		X	X	X	X	X
Concomitant Medication	X	X	X	X	X	
Physical Exam	X	X			X	
Nasal Exam	X	X	X	X	X	X[d]
Vital Signs	X	X	X	X	X	X
12-Lead ECG	X	X	X	X	X	
Blood Hematology-Central	X				X	X[f]
Blood Chemistry-Central	X[e]	X[e]	X[e]	X[e]	X[e]	X[e,f]
Urinalysis-Central	X	X	X	X	X	X[f]
Pregnancy Test[g]	X	X	X	X	X	X
Urine Drug Test[h] (UDT)-Central	X					
Thyroid Stimulating Hormone (TSH)-Central	X					
HbA1c	X					

Study Phase	**Screening/Washout (Up to 21 days)** **Run-In (At least 28 days*)**	**Treatment 84 days**				**Follow-up[b] 14 days**
Study Visit	**V1 Screening**	**V2 Baseline/ Randomization**	**V3**	**V4**	**V5 Or Early Termination[a]**	**Visit 6 End-of-Study In-Person**
Study Week			**Week 4**	**Week 8**	**Week 12**	**Week 14**
Study Days	**Day** -49 to Day -1	**Day 1**	**Day 29 ± 4d**	**Day 57 ± 4d**	**Day 85 ± 4d**	**Day 99 ± 4d**
Optional Pharmacogenomics		X	*[s]	*[s]	*[s]	*[s]
C-SSRS[i]	X	X	X	X	X	X
MSI-BPD[j]	X					
Randomization		X				
Placebo Response Training	X[t]	X	X	X	X	
E-diary Training[k]	X	X	X	X		
E-diary Assessment[l]	X	X	X	X		
Dispense Study Drug		X[m]	X	X		
Return study drug and Perform Accountability			X	X	X	
Review e-diary		X	X	X	X	
PGIC[n]			X	X	X	
HADS[o]		X	X	X	X	
MIDAS[p]		X			X	
MSQ[q]		X	X	X	X	
CSFQ-14[r]		X			X	

* Any extension beyond 28 days is only allowed for scheduling purposes or e-diary compliance due to technical issues and up to a maximum of 7 days.

[a] An Early Termination Visit will be conducted approximately 7 days (+3 days) of withdrawing from study

[b] Follow-up visit will be conducted approximately 14 days (± 4 days) after Visit 5
[c] Record any changes to the medication history obtained at Screening
[d] Nasal exam will only be performed at Visit 6 if any abnormality on exam at Visit 5 or any report of a nasal cavity AE
[e] Chemistry panel only: triggered serum osmolality will be measured from same specimen if sodium is below the lower limit of normal
[f] Urinalyses, hematology and chemistry labs will only be repeated at Visit 6 if clinically significant findings were observed at Visit 5
[g] Women of childbearing potential only: screening serum pregnancy test will be analyzed at Central laboratory; consecutive urine pregnancy tests will be conducted on-site at every subsequent study visit
[h] Urine drug test: cocaine, phencyclidine (PCP), barbiturates, amphetamines, cannabis, and opiates
[i] C-SSRS: Columbia Suicide Severity Rating Scale
[j] MSI-BPD: McLean Screening Instrument for Borderline Personality Disorder
[k] E-diary training will be conducted at Visit 1 (Screening Visit) and Visit 2 (Treatment) and will be repeated at Visits 3 and 4. E-diary is collected at Visit 5
[l] Patients will start completing their e-diary the day after their Screening Visit.
[m] Study drug administration training performed at Visit 2 in addition to dispensation of study drug
[n] PGIC: Patient Global Impression of Change
[o] HADS: Hospital Anxiety and Depression Scale
[p] MIDAS: Migraine Disability Assessment questionnaire
[q] MSQ: Migraine-Specific Quality of Life Questionnaire v2.1
[r] CSFQ-14: Changes in Sexual Functioning Questionnaire Short-Form
[s] Pharmacogenomics should be drawn at Baseline but if it is not drawn, drawing at a subsequent visit is allowed.
[t] Placebo Response training will be conducted in the form of a video that patients watch at Visit 1. At subsequent visits (V2-V5), training will be conducted via a paper script that the site staff reviews with the patient.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ALT	alanine aminotransferase (SGPT)
ANOVA	analysis of variance
AP	alkaline phosphatase
AST	aspartate aminotransferase (SGOT)
BID	twice daily
BMI	body mass index
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
CM	Chronic migraine
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSFQ-14	Changes in Sexual Functioning Questionnaire Short-Form
CV	coefficient of variation
DMP	data management plan
DOB	date of birth
EM	Episodic migraine
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Hct	hematocrit
Hgb	hemoglobin
HIPAA	Health Information Portability and Accountability Act
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
mITT	modified intent-to-treat
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-Effects Model of Repeated Measures
ms	millisecond(s)
MSI-BPD	McLean Screening Instrument for Borderline Personality Disorder
NDA	New Drug Application
NSAIDs	Non-steroidal anti-inflammatory drugs
OTC	over-the-counter
PRN	pro re nata (as needed)
PRO	patient-reported outcome
QD	once daily
RBC	red blood cell (count)
SAE	serious adverse event

SD	standard deviation
SE	standard error
SF	screen failure
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
TEAE	Treatment-Emergent Adverse Event
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
WBC	white blood cell (count)
WoCBP	women of childbearing potential

1 INTRODUCTION

Migraine affects an estimated 14.7% of the world's population (Steiner, et al., 2013) and is ranked sixth by the World Health Organization as the cause of years lost due to disability (WHO, 2016). Chronic migraine (CM) is defined by the International Classification of Headache Disorders 3rd edition (ICHD-3) as headache occurring on ≥ 15 days/month for > 3 months with features of migraine on ≥ 8 days/month. CM affects approximately 2% of the world's population with prevalence 2.5 to 6.5 times higher in women (1.7 to 4.0%) than in men (0.6 to 0.7%) (Natoli, et al., 2010). While migraine therapy has improved significantly since the introduction of serotonin 5-HT_1-receptor agonists (i.e., triptans) and more recently, monoclonal antibodies to calcitonin gene-related protein (CGRP) or small molecule inhibitors to its receptor, a substantial number of patients continue to be treated inadequately.

The pathophysiology of CM is not fully understood, but there is evidence that functional changes occur in the brain including increased cortical hyperexcitability, central trigemino-thalamic sensitization, and defective descending pain modulatory activity (Mathew, 2011; Su and Yu, 2018). It is postulated that recurring episodic migraine (EM) (Goadsby, et al., 2017) and comorbid conditions, such as medication overuse or anxiety/depression, may lead to dysfunction of pain modulation pathways, with reduced nociceptive thresholds and atypical release of nociceptive molecules. This may cause increased central sensitization of the trigeminal and thalamic neurons, with little recovery between attacks, leading to progression from EM to CM. CGRP is involved in pain modulation, perception and sensitization, and has a major role in the pathogenesis of migraine (Ho, et al., 2010; Edvinsson, 2015). Activation of transient receptor potential channels, which coexist with CGRP in the same nociceptive neurons, promotes excitation of the trigemino-vascular pathway, release of CGRP, and pain (Benemei, et al., 2013; Benemei, et al., 2014; Dussor, et al., 2014).

Oxytocin is a nonapeptide produced in the supraoptic and paraventricular nucleus of the hypothalamus which is released into the systemic circulation through the posterior pituitary gland (Moller, 2021). There are also collateral oxytocin producing neurons from the hypothalamus that project to diverse brain regions such as nucleus accumbens and amygdala. Oxytocin's physiological functions include regulation of uterine contractility in pregnant women and milk ejection in lactating women. In the central nervous system (CNS), oxytocin is a mediator of pro-social behavior and fear response. Oxytocin is approved by the Food and Drug Administration (FDA) for intravenous use to induce labor in pregnant women as well as for the treatment of postpartum hemorrhage. Intranasal oxytocin is used in Europe for inducing labor in pregnant women and for enhancing milk production in lactating women.

Oxytocin exerts analgesic effects when administered intrathecally in the rodent model. This effect appears to be receptor specific since it was blocked by an oxytocin antagonist (Tzabazis, et al., 2017). The therapeutic index of intrathecal oxytocin is large, i.e., 270-fold when considering analgesic versus severe side effects and 400-fold when considering analgesic effects versus lethality. Oxytocin is thought to mediate its analgesic action in part via the endogenous opioid system. Diverse CNS sites may be involved in mediating such

analgesic effects, since oxytocinergic neurons display widespread projections throughout the CNS.

Nonclinical studies have confirmed that oxytocin accumulates in the ganglion of the trigeminal nerve after intranasal administration in rats (Tzabazis, et al., 2017). These rats showed site-specific analgesic effects when stimulated in the face (innervated by the trigeminal nerve) but not when stimulated at the hind paw.

A single study in humans suggested that intrathecal injection of oxytocin may prove useful as an analgesic treatment modality. Oxytocin reduced back pain in dose-dependent fashion and a dose of 0.5 IU/kg of oxytocin provided complete relief in about 83% of patients studied (Yang, 1994).

[redacted]

This current study is a proof-of-concept study examining whether administration of intranasal oxytocin is effective in the preventive treatment of migraine headache. Intranasal administration of drugs may preferentially target the CNS, thereby allowing local administration of lower drug doses for achieving effective concentrations thereby attenuating risk of systemic side effects.

2 STUDY OBJECTIVES

- Evaluate the efficacy of 2 TNX-1900 (intranasal oxytocin) treatment regimens at 30 IU daily (QD) and 30 IU twice daily (BID) compared to placebo in chronic migraineurs.
- Evaluate the safety and tolerability of 2 TNX-1900 (intranasal oxytocin) treatment regimens at 30 IU QD and 30 IU BID compared to placebo in chronic migraineurs.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a double-blind, randomized, placebo-controlled, multicenter, 3 arm parallel Phase 2 study. Men and women with a current diagnosis of CM according to the International Classification of Headache Disorders, 3rd edition (ICHD-3) and who meet the study entry criteria will enter a Screening Period followed by a Run-in Period. A Run-in Period is a prospective baseline observation in which patient's migraine/headache activity will be recorded for at least 28 days. At the end of the Run-in Period, eligible patients will be randomized at a 1:1:1 ratio, to one of the 3 treatment arms: TNX-1900 at a fixed daily dose of 30 IU QAM / placebo QPM (Treatment Arm A), or fixed daily dose of 30 IU QAM / 30 IU QPM (Treatment Arm B), or placebo QAM / placebo QPM (Treatment Arm C), for the duration of a 12-week Treatment Period. Randomization will be stratified by study site and preventive migraine medication (use of a single preventative vs. no preventative). All participants will administer study drug twice a day, mornings and evenings, in a double-blind design. Two vials of study drug are dispensed at each dispensing visit, one clearly marked for "MORNING" and one clearly marked for "EVENING".

The study will be conducted in 3 periods (Screening/Wash-Out/Run-In, Treatment, and Safety Follow-up) and will consist of at least 6 visits (Screening Visit, Randomization/Baseline Visit, 3 Treatment Visits, and a Safety Follow-up Visit).

Screening/Washout/Run-In Period (Visit 1: Screening Visit)

After providing written informed consent, patients will be assessed for eligibility (considering medical history, migraine headache history, medication use, physical exam, nasal exam, vital signs, clinical labs and electrocardiogram [ECG]).

Eligible patients will be trained on the e-diary during the Screening Visit and will enter a 28-day Run-In period which will last for at least 28 days. Patients who need to wash out excluded medications will have up to an additional 21 days in the Run-In period, but every effort should be made to minimize to the fewest days needed for the given washout period(s) in the protocol.

During the Run-In, patients will be required to answer questions daily regarding headaches and rescue (abortive) medication use on an electronic diary (e-diary) regardless of whether patients experienced a headache on that day. It is a patient's responsibility to be compliant with e-diary entries. Each patient's headache frequency, as well as e-diary compliance, will be evaluated at the end of the Run-in Period to ensure the patient meets all required eligibility criteria for treatment randomization. The patient **must not** be informed of the minimum number of headache days and migraine headache days required to enter the study as this might bias entries to the e-diary during Run-in Period**.**

It is important to note that the last 28 days of Run-In diary entries includes diary entries logged on morning of the Baseline Visit. Patients should be reminded to complete the required e-diary entries on the morning of the Baseline Visit.

During this period, if any test results come back and indicate a patient's ineligibility for the study, the patient should be considered a SF and informed that they are not eligible for the study and can stop completing the e-diary. However, if the investigator determines that the patient should be brought back into the clinic for re-testing, the patient should continue completing the e-diary until a final determination regarding eligibility is made.

Any patients not meeting the randomization criteria at the end of the Run-in Period will be considered a SF.

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

Double-blind Treatment Period (Visit 2: Randomization/Baseline; Visits 3, 4, 5: Treatment)

The Treatment Period will last for about 84 days. At Visit 2, eligible patients will be randomized in a 1:1:1 ratio to one of 3 treatment arms (A, B or C) as summarized above. Randomization will be stratified by study site and concomitant migraine preventive medication (use of a single preventative vs. no preventative). Patients will be required to answer daily headache questions and study drug compliance on an e-diary during the Treatment Period regardless of whether a headache was experienced that day.

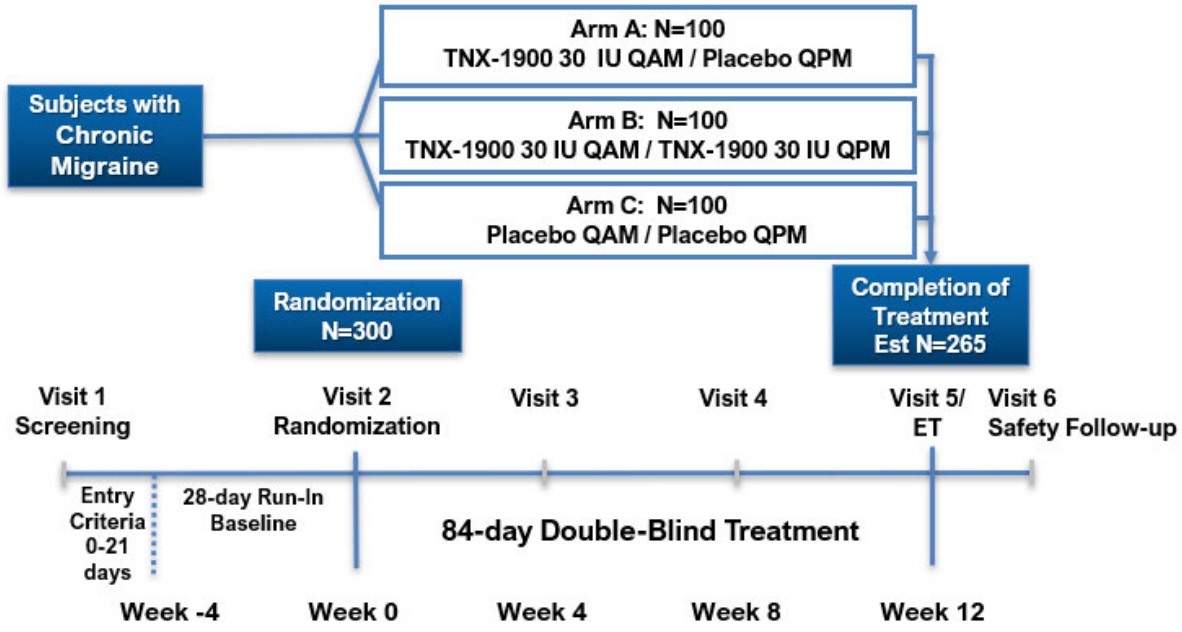
All patients who withdraw early from the study will be encouraged to complete an Early Termination Visit for safety evaluations (Visit 5 [V5]) within 7 days of withdrawal from the study. Study end is after Visit 5/ET. A Safety Follow-up Visit (Visit 6 [V6]) will occur 14 days after V5/ET.

Safety Follow-up Period (Visit 6)

Approximately 14 days (+4 days) after Visit 5 or End of Treatment (ET), all randomized patients will attend a Safety Follow-up Visit.

A schema of the study design is provided in Figure 1.

Figure 1 Study Schema



3.2 Rationale for Study Design and Placebo Group

The formulation of TNX-1900 has been designed specifically for intranasal administration, and regimens of daily or twice daily administration of TNX-1900 are being investigated as potential preventive treatments for migraines in a population with CM. Additional details regarding the nonclinical studies supporting the mechanism of action in migraine and the clinical experience from early clinical studies carried out to date with intranasally-delivered oxytocin can be found in the Investigator's Brochure.

3.3 Study Duration and Dates

The study duration for each patient will be approximately 18-21weeks including the 14-day Safety Follow-up Period.

4 STUDY POPULATION SELECTION

4.1 Inclusion Criteria for Enrollment

1. Men and women aged 18 to 65 years, inclusive, at the time of Visit 1.

2. History of migraine with or without aura for at least 1 year and onset at < 50 years of age. Patient must also have a history of chronic migraine > 3 months prior to Visit 1 as defined by IHS ICHD-3 (Appendix A)

3. Able to differentiate migraine or probable migraine headache from other headaches.

4. Patients can be on stable ≤ 1 preventive medication and any number of abortive migraine medications for 90 days prior to Screening and during the study. All treatments, other than the study drug, thought to have preventive efficacy in migraine should not be started or discontinued during the entire study period. *Note: Up to approximately 30% of the patients randomized into the study can be on 1 preventative medication. Once this category is filled, only patients who are not on any preventative medications can be randomized into the study. From study start, sites should enroll patients into both categories in parallel until informed otherwise.*

5. If female, is either not of childbearing potential (defined as postmenopausal for at least 1 year or surgically sterile [e.g., 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. Bilateral tubal ligation

    d. Double-barrier method (condoms, sponge, diaphragm, or vaginal ring with spermicidal jelly or cream).

    e. Partners of vasectomized (> 1 year ago) males in monogamous relationships.

    f. Females involved only in same sex relationships.

    g. Females practicing abstinence may have the birth control requirement waived only with Medical Monitor approval.

6. If male, is either vasectomized (> 1 year ago) or will be practicing once of the following methods of birth control throughout the study:

    a. Partner in monogamous relationship with female practicing one of the methods in 5a or 5b above.

b. Double-barrier method (condoms, sponge, diaphragm, or vaginal ring with spermicidal jelly or cream.)

c. Males involved only in same sex relationships.

d. Males practicing abstinence may have the birth control requirement waived only with Medical Monitor approval.

7. The patient is willing and able to comply with all protocol-specified requirements.

8. Capable of reading and understanding English and able to provide written informed consent to participate.

4.2 Exclusion Criteria for Enrollment

Patients who meet any of the following criteria will be excluded from the study.

1. History of cluster headache.

2. Presence of headaches more than 26 days a month on an average for the 6 months prior to Screening.

3. Failed to benefit from an adequate dose and duration, in the investigator's judgment (e.g., one month of β-blocker), of 3 or more migraine preventive medications.

4. History of seizure disorder other than childhood febrile seizures.

5. The patient is at increased risk of suicide based on the investigator's judgment, 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. In general, chronic use of systemic steroidal or non-steroidal anti-inflammatory drugs (NSAIDs) and combination products containing NSAIDs for any indication will be prohibited during the Screening Period and during the study. The following instructions should be followed:

   a. Excepting topical usage, chronic use of systemic steroidal anti-inflammatory drugs is not allowed for any indication.

   b. Chronic use of NSAIDs on a daily basis is not allowed; therefore, those on daily NSAIDs necessary for treatment of other medical conditions, e.g., arthritis, should not be enrolled; NSAIDs may be used as needed (PRN) for headache pain only if they are part of patient's typical migraine/headache abortive treatment regimen; other use of NSAIDs is allowed as needed for other acute pain syndromes, but daily use is not allowed.

7. Use of opiates or barbiturates more than 4 days for more than 3 consecutive months prior to Visit 1 and during the study.

8. Use of the following non-pharmacological treatments for headache or any other indication, is prohibited within 90 days prior to Screening and throughout the entire study: any electrical or magnetic stimulating devices (e.g., non-invasive vagal nerve stimulation (GammaCore), transcranial magnetic stimulation (TMS Mini), or Remote Electrical Neuromodulation [REN or Nerivio]). Any types of psychotherapy, stress management, acupuncture, chiropractic manipulation, and physical therapy is prohibited within 90 days of Screening and throughout the entire study **only** if the treatment is specifically targeted for the relief of headaches, migraines, or any type of head and neck pain. Otherwise, such treatments must have been ongoing for at least 90 days prior to Visit 1 with a plan to continue throughout the study to be eligible. Also, occipital nerve blocks or botulinum toxin treatments for any indication are prohibited within 90 days of Screening and throughout the entire study

9. Use of OTC nasal products (i.e., saline spray, Neti-Pot, Naväge®, etc.) during the study.
10. History of unstable psychiatric illness requiring hospitalization in the 12 months prior to Visit 1. Coexisting conditions, such as depression and anxiety, may be included if they are stable on current treatment regimens (with no change in treatment regimen for the last 90 days) and no planned changes during the study.

11. History of or evidence supporting 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) and/or the investigator's opinion.

12. Body Mass Index (BMI) > 40 kg/m^2.

13. Any clinically significant medical condition that, in the opinion of the investigator, would make the patient unsuitable for study participation and completion.

14. Any use of intranasal corticosteroid medications or conditions in which use of intranasal corticosteroids may be indicated during the study, e.g., unstable allergic rhinitis that has previously required intranasal corticosteroids. Intranasal corticosteroid use is not allowed within 28 days of Baseline/Randomization/Visit 2 and during the treatment phase or follow-up period of the study.

15. Clinically significant laboratory and ECG abnormality (in the investigator's opinion) based on Screening laboratory tests, or any of the following:

    a. Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 2 times the upper level of normal (ULN)

    b. Creatinine > 1.2 times the ULN

    c. Thyroid stimulating hormone (TSH) > 1.5 times the ULN

d. HbA1c > 7.5%

e. Resting heart rate ≤ 45 bpm or ≥ 100 bpm

f. Clinically significant arrhythmia or heart block

g. Corrected QT interval by the Fridericia formula (QTcF) > 470 ms for females; and > 450 ms for males.

16. History of chronic nasal obstruction or local pathology in nostril pathway which, in the opinion of the investigator, would prevent appropriate nasal administration of the study drug.

17. Known allergy or hypersensitivity to oxytocin containing products.

18. Positive results for illegal or abused substances other than cannabis/ tetrahydrocannabinol at Screening or Baseline.

19. Women who are pregnant, planning to become pregnant, or nursing during the study.

20. Currently enrolled in or have participated within the last 30 days in a clinical trial involving an investigational product prior to Visit 1 (does not apply to anti-CGRP agent studies covered in Exclusion 21).
21. Patients who recently discontinued treatment with an anti-calcitonin-gene-related peptide (CGRP) antibody or participated in an anti-CGRP antibody clinical study must be at least 4 months from the last drug administration prior to Visit 1. Patients who are in an extended observational period from such an anti-CGRP antibody study and are at least 4 months from the last drug administration prior to Visit 1 are eligible. Small molecule anti-CGRP treatments, e.g., gepants, are treated similarly but only must be at least 1 month from last drug administration prior to Visit 1.

22. History of clinically significant and currently relevant cardiovascular disease or vascular ischemia (including myocardial, cerebral, peripheral extremity or other ischemic event) or thromboembolic events (arterial or venous thrombotic or embolic events) such as cerebrovascular accident, deep vein thrombosis, or pulmonary embolism. Recent myocardial infarction (within the last 2 years). Diagnosed with heart failure.
23. History of alcohol or drug abuse within the prior year, or alcohol or drug dependence within the prior 5 years, as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).

4.3 Eligibility Criteria for Randomization

Up to approximately 30% of the patients randomized into the study can be on 1 migraine preventative medication. Once this category is filled, only patients who are not on any

preventative medications can be randomized into the study. *From study start, sites should enroll patients into both categories in parallel until informed otherwise.*

For a patient to be eligible for randomization, the following should be observed during the last 28 days of the Run-in Period:

1. Demonstrate an ability to properly use e-diary.
2. Complete ≥ 82% of the e-diary daily entries (23 days out of 28-day period).
3. At least 14 headache (migraine-like or tension-type-like) days
4. At least 8 days

- An attack lasting 4 hours or more and meeting the ICHD-3 criteria (diagnostic criteria C and D) for migraine without aura (Appendix A)
- Migraine with aura
- Probable migraine (a migraine subtype fulfilling all but one criterion (B-D) for migraine without aura)
- An attack of any duration that was believed by the patient to be a migraine and was relieved by a triptan, ergot derivative, or other migraine-specific abortive medication.

It is important to note that the last 28 days of Run-In diary entries includes diary entries logged on morning of the Baseline Visit. Patients should be reminded to complete the required e-diary entries on the morning of the Baseline Visit.

Those patients who only miss the e-diary compliance requirement (i.e., compliance less than 82%) and otherwise are qualified for randomization may be given the opportunity to either extend or repeat the Run-in Period. Any extension will be considered on a case-by-case basis and require medical monitor approval.

On the day of the Baseline/Randomization Visit (V2), patients must still meet all inclusion criteria and none of the exclusion criteria and be in good general health, or with only stable and non-serious conditions that, in the opinion of the investigator, will not place the patient at risk.

4.4 Withdrawal of Patients

Patients may be withdrawn from the Run-in Period prior to the end of 28-days if patients were determined mathematically to be unable to meet the headache criteria required by the protocol.

The investigator may withdraw a patient from the trial for any of the following reasons:

- A protocol violation occurs,
- A serious or intolerable adverse event occurs,
- A clinically significant change in a laboratory parameter occurs,

- The sponsor or investigator terminates the study,
- The patient requests to be discontinued from the study.

In addition, any patient has the right to withdraw from the study at any time for any reason.

All patients who withdraw early from the study will be encouraged to complete the ET Visit for safety evaluations (Visit 5) within 7 days from withdrawal of study, followed by a Safety Follow-up Visit (Visit 6) approximately 14 days from the last study drug administration.

5 STUDY TREATMENT(S)

5.1 Description of Treatment(s)

5.1.1 Study Drugs

5.1.1.1 TNX-1900

TNX-1900 is provided as a preservative-free, aqueous, oxytocin containing solution for intranasal delivery. TNX-1900 will be supplied at a 150 IU/mL oxytocin concentration for this study. One dose of study drug administration requires 2 administration sprays into the nostrils (1 spray to each nostril). Given the 150 IU/mL concentration, each 0.10 mL spray delivers 15 IU of TNX-1900, respectively. Consequently, one dose (2 sprays- one spray per nostril) equates to a 30 IU oxytocin total dose.

5.1.1.2 Placebo

Placebo is provided as a preservative-free, colorless aqueous solution containing the same excipients as TNX-1900, minus oxytocin. Administration instructions are identical to those for TNX-1900. Intranasal application bottles containing placebo will deliver 0.10 mL volume per spray. A dose of placebo will comprise 1 spray per nostril (2 sprays total).

A brief training on placebo response will be given to patients at Visits V1, V2, V3, V4, and V5.

5.2 Treatments Administered

During the double-blind Treatment Period, patients are instructed to self-administer ONE dose (2 sprays total, 1 spray per each nostril) of MORNING study drug at a fixed time in the morning and ONE dose (2 sprays total, 1 spray per each nostril) of EVENING study drug at a fixed time in the evening, with a minimum period of 6 hours between the morning and evening doses. Each patient will be dispensed 2 bottles of study drug at each visit at which study drug is dispensed. The nasal spray bottle of MORNING study drug will be clearly labeled ‘MORNING’, and the EVENING study drug will be clearly labeled ‘EVENING’.

Study drug administration should occur as follows:

Dose	Treatment	Administration
30 IU QAM / Placebo QPM	A	1 dose from ‘MORNING’ nasal spray bottle = 1 spray each nostril of TNX-1900 (2 sprays total) 1 dose from ‘EVENING’ nasal spray bottle = 1 spray each nostril of placebo (2 sprays total)
30 IU QAM / 30 IU QPM	B	1 dose from ‘MORNING’ nasal spray bottle = 1 spray each nostril of TNX-1900 (2 sprays total) 1 dose from ‘EVENING’ nasal spray bottle = 1 spray each nostril of TNX-1900 (2 sprays total)

Dose	Treatment	Administration
Placebo QAM / Placebo QPM	C	1 dose from 'MORNING' nasal spray bottle = 1 spray each nostril of placebo (2 sprays total) 1 dose from 'EVENING' nasal spray bottle = 1 spray each nostril of placebo (2 sprays total)

Patients will be trained in the use of the nasal applicator prior to home use and will receive an Instructions for Use document.

Priming of each dispensed bottle should be conducted by site staff at V2, V3, and V4.

Prior to leaving the clinic at Baseline/Randomization/Visit 2, the patient will take their first dose from the Morning dose bottle regardless of time of day. Also, on the night of Visit 2, patients should administer from the Evening dose bottle the same evening at home, with a minimum period between the two doses of at least 6 hours.

At subsequent visits (V3, V4, V5), the patient should take their AM dose of study drug from their existing study drug bottle, prior to the site collecting it and dispensing new study drug bottles. Patients should be reminded to take the AM dose prior to arriving at the clinic if possible.

5.3 Method of Assigning Patients to Treatment Groups

Approximately 300 eligible patients will be randomized at a 1:1:1 ratio, to one of the 3 treatment arms receiving TNX-1900 at a fixed daily dose of 30 IU QD (Treatment Arm A) or fixed daily dose of 30 IU BID (Treatment Arm B) or receiving placebo (Treatment Arm C) for the duration of a 12-week Treatment Period. Randomization will be stratified by study site and use of one concomitant preventive migraine medication (vs. no concomitant preventive migraine medication). All participants will administer study drug twice a day (mornings and evenings) in a double-blind design.

The randomization schedule will be computer generated using a permuted block algorithm and will randomly allocate study drug to randomization numbers. The randomization numbers will be assigned through a central interactive web response system (IWRS) as patients are entered into the study.

5.4 Blinding and Unblinding

All patients, Investigators, and study personnel involved in the conduct of the study, including data management, will be blinded to treatment assignment except for a specified unblinded statistician and programmer from the study contract research organization (CRO) who will have access to the randomization code. The unblinded study personnel will not participate in study procedures or data analysis prior to unblinding of the study data to all study-related personnel after database lock and only upon written notification by the sponsor. If an interim analysis is conducted, then unblinded personnel who are not otherwise involved in the study will prepare the data for review.

Study personnel will make every effort to safeguard the integrity of the study blind to minimize bias in the conduct of the study. Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding will be permitted in a medical emergency that requires immediate knowledge of the patient's treatment assignment.

Unblinding should be discussed in advance with the medical monitor, if possible. For emergency unblinding, study personnel will use the IWRS. If the investigator is not able to discuss treatment unblinding in advance, they must notify the medical monitor as soon as possible about the unblinding incident without revealing the patient's treatment assignment.

Unblinding for an individual patient will not result in unblinding the treatment assignments for the remaining patients in the study. Thus, the overall study blind will not be compromised. If a patient's treatment assignment is unblinded, he/she may or may not be asked to withdraw from the study. The investigator will make this decision after consultation with the medical monitor.

5.5 Concomitant Therapy

Patients can be on stable ≤ 1 preventive medication and any number of abortive migraine medications for at least 90 days prior to Screening. Up to approximately 30% of the patients randomized into the study can be on 1 preventative medication. Once this category is filled, only patients who are not on any preventative medications can be randomized into the study. *From study start, sites should enroll patients into both categories in parallel until informed otherwise.*

All treatments, other than the study drug, thought to have preventive efficacy in migraine should not be started or discontinued during the entire study period. 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 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.

Chronic use of NSAIDs daily is not allowed, therefore those on daily NSAIDs necessary for treatment of other medical conditions (e.g., arthritis), should not be enrolled. NSAIDs may be used as needed for abortive migraine treatment **only if they are part of the patient's typical migraine/headache abortive treatment regimen**. Other use of NSAIDs is allowed **as needed** for other acute pain syndromes, but daily use is not allowed. Use of ibuprofen for such PRN use of NSAIDs is preferred over longer acting NSAIDs, e.g., naproxen and celecoxib. 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.

5.5.1 Permitted Therapy

The array of medications a patient typically uses for abortive treatment of a migraine should be established at the Screening Visit and recorded as PRN concomitant medications.

Although any number of abortive medications are permitted, no *new* abortive medications should be started at any time during participation in the protocol. As noted above, PRN use of NSAIDs as part of a patient's typical migraine abortive regimen or for treatment of other acute pain syndromes is permitted. Ibuprofen is preferred for such PRN use of NSAIDs over longer acting NSAIDs, e.g., naproxen and celecoxib.

5.5.2 Prohibited Therapy

Use of opioids or barbiturates for more than 4 days per month; systemic corticosteroids, intranasal corticosteroids, and chronic daily NSAIDs (except permitted uses outlined in Section 5.5.1), are prohibited. Additionally, use of intranasally administered over the counter products (Flonase) is also prohibited during this study. Any use of nasal irrigation, e.g., "neti pot" or similar, is prohibited during this study.

5.6 Restrictions

5.6.1 Prior Therapy

Patients who are taking certain medications to manage their migraine 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. This applies to any patient who is taking greater than one migraine preventive medication.

5.6.2 Fluid and Food Intake

There are no restrictions on fluid or food intake in this study.

5.6.3 Reproductive Restrictions

All patients of childbearing potential who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during treatment. Patients should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected.

Participants of reproductive potential must agree to use a highly effective method of contraception from the time of consent and for 28 days following his or her last dose of investigational product (IP). Highly effective methods of contraception are as follows:

1. If female is either not of childbearing potential (defined as postmenopausal for at least 1 year or surgically sterile [e.g., bilateral oophorectomy, or hysterectomy]):
   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. Bilateral tubal ligation

d. Double-barrier method (condoms, sponge, diaphragm, or vaginal ring with spermicidal jelly or cream).

e. Partners of vasectomized (> 1 year ago) males in monogamous relationships.

f. Females involved only in same sex relationships.

g. Females practicing abstinence may have the birth control requirement waived only with Medical Monitor approval.

2. If male:

a. Partner in monogamous relationship with female practicing one of the methods in a) or b) above.

b. Double-barrier method (condoms, sponge, diaphragm, or vaginal ring with spermicidal jelly or cream.)

c. Males involved only in same sex relationships.

d. Males practicing abstinence may have the birth control requirement waived only with Medical Monitor approval.

Pregnancy testing will be conducted prior to administration of the IP on every patient of childbearing potential. A patient who is found to be pregnant at the Screening Visit will be excluded from the study and considered to be an SF. A patient who becomes pregnant during IP treatment will be immediately discontinued from study participation. See Section 7.2.8.2 for additional details.

5.7 Treatment Compliance

Treatment compliance will be monitored via the e-diary. The e-diary will be used to log headaches and abortive medications, but once patients are randomized into the study and starts the study drug, they will also be required to report whether they have taken their morning dose and evening dose on a daily basis. Please refer to Section 6.8.5 for additional details on the e-diary.

5.8 Packaging and Labeling

Study drug supplies will be packaged identically to maintain the integrity of the study blind. The study drug bottles will be labeled minimally with the following information: study protocol number, sponsor name and location, bottle number, storage conditions, usage instructions (intranasal use only), and caution statements for an investigational drug, i.e., “Caution: New Drug - Limited by Federal (or United States) law to investigational use”.

5.9 Dispensing, Storage and Accountability

The study drugs will be supplied by Tonix or a designee to be used exclusively in the clinical study according to the instructions in this protocol. The investigator is responsible for dispensing the study drugs according to the dosage scheme and for ensuring proper storage of the products.

Until study drug is dispensed to the patients, it must be stored in a securely locked refrigerated area that is not generally accessible. The key to the storage area is to be kept by the investigator or designee responsible for the study drug. The storage will be accessible only to those persons authorized by the investigator to dispense the products.

The investigator or designee must confirm the receipt of the IP with his or her signature. A copy of this receipt must be kept by the investigator and another copy will be stored at Tonix or its designee.

The investigator or investigator designee must maintain adequate records showing the receipt, dispensing, return, or other disposition of study drugs, including the date, quantity, batch or code number, and identification of patients who received each bottle of study drug. The investigator will not supply study drugs to any person except those named as sub-investigators on the FDA form 1572, designated study personnel, and patients in this study. The investigator will not dispense the study drugs from any study sites other than those listed on the FDA form 1572. Study drugs may not be relabeled or reassigned for use to other patients. If any of the study drug is not dispensed, or is lost, stolen, spilled, unusable, or received in a damaged container, this information must be documented and reported to the sponsor and appropriate regulatory agencies, as required.

Upon completion of the study, all study drug (partly used, unused, and empty packaging, e.g., vials with intranasal applicators) must be left in the original packaging and shipped back to drug depot.

6 STUDY PROCEDURES

6.1 Informed Consent

Before the potential participant 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.

The patient will also be provided with the opportunity to sign a separate consent form for the optional pharmacogenomics blood draw and analysis. Participation in this optional portion of the study is not required. Ideally, the blood draw for the optional pharmacogenomics should be drawn at the Baseline visit; however, it can be drawn at a subsequent visit if needed. A patient can decide to decline the optional pharmacogenomics but still participate in the main study.

6.2 Medical, Psychiatric and Medication History

Any clinically significant abnormal findings at Screening will be recorded in medical history. Any changes to the medication history obtained at Screening will be recorded at Baseline/Randomization/Visit 2. (For further details: Schedule of Assessments

). A self-assessed MSI-BPD will be administered to rule out BPD, as per Exclusion 11 (Section 4.2).

6.3 Physical Examination

A complete physical examination will be performed at Visits V1, V2 and V5. The complete physical examination may exclude rectal, genitourinary, and breast examinations for female patients, and rectal and genitourinary examinations for male patients. Examination of male patients should include breast examination at Visits V1, V2, and V5 in order to monitor for the unlikely adverse event of gynecomastia.

6.4 Nasal Examination

A nasal examination will be performed at Visit 1, Visit 2, Visit 3, Visit 4, and Visit 5. The nasal exam will be conducted using a nasal speculum and headlamp to view into each nostril in order to establish any baseline pathology and assess any clinically significant changes in the nasal passages. A nasal exam should only be conducted at Visit 6 if needed to follow up on unresolved findings from the Visit 5 examination.

6.5 Vital Signs

Vital signs (sitting blood pressure and heart rate, temperature) and weight will be assessed at Visits V1, V2, V3, V4, V5, and V6. Height will be measured without shoes at Visit 1 only. The BMI will be a derived variable, based on height and weight entries obtained at the Screening Visit.

6.6 Electrocardiogram (ECG)

An ECG will be conducted at V1, V2, V3, V4, and V5. PR intervals, QRS intervals, QT interval, and QTcF will be collected. An investigator interpretation of the ECG will also be required: normal, abnormal- non-clinically significant, abnormal- clinically significant.

6.7 Clinical Laboratory Tests

6.7.1 Laboratory Parameters

Patients will be in a seated or supine position during blood collection. Clinical laboratory tests will include the following:

Table 1. List of Laboratory Tests

Serum Chemistry	
Alkaline phosphatase	Creatine kinase (CK)
Alanine aminotransferase (ALT; SGPT)	Glucose
Aspartate aminotransferase (AST/SGOT)	LDH
Blood urea nitrogen (BUN)	Phosphorus
Bilirubin (direct and total)	Potassium
Calcium	Sodium (serum osmolality will also be tested if Sodium is below the lower limit of normal)
Carbon dioxide (CO_2)	Protein (total)
Chloride	Triglycerides
Creatinine	Uric Acid
Hematology	
Hematocrit (Hct)	Mean corpuscular volume (MCV)
Hemoglobin (Hgb)	Platelet count
Mean corpuscular hemoglobin (MCH)	Red blood cell (RBC) count

Serum Chemistry	
MCH concentration (MCHC)	WBC differential
Other	
Thyroid Stimulating Hormone (TSH)	Hemoglobin A1c (HbA1c)

Urinalysis:

Urinalysis will include assessment or measurement of the following:

Appearance, Bilirubin, Color, Glucose, Ketones, Microscopic Examination, Nitrite, Occult blood, pH, Protein, Specific Gravity, Urobilinogen

Urine Drug Test:

Cocaine, phencyclidine (PCP), barbiturates, amphetamines, cannabis, and opiates.

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 other than cannabis (e.g., cocaine, methamphetamine) or due to a nondisclosed opioid, amphetamine, or barbiturate, then he/she should be deemed an SF.

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

Serum Pregnancy Test:

A test for serum human chorionic gonadotropin (hCG) (only for females who are not diagnosed as postmenopausal for greater than one year or not of childbearing potential) is sent to the central lab at the Screening Visit 1 only.

Urine Pregnancy Test:

Urine hCG, for females who are not diagnosed as postmenopausal or not of childbearing potential, is conducted on-site at **all study visits after** the Screening Visit.

6.7.2 Sample Collection, Storage, and Shipping

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.

6.7.3 Abnormalities

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 its designee should be notified. Clinically significant abnormalities in laboratory values after the Screening will be recorded as AEs.

NOTE: A Screening TSH level greater than 1.5 times higher than the ULN, or ALT or AST level > 2x ULN, is exclusionary; however, the patient may remain in Screening to undergo repeat liver function tests if a transient abnormality (e.g., viral illness; effects of a medication being discontinued, etc.) is thought to be responsible for their initial elevation.

6.8 Efficacy Assessments

Many of the secondary and exploratory efficacy endpoints in this study are derived from patientive 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 should review the responses for completeness with the patient.

6.8.1 Patient Global Impression of Change

The Patient Global Impression of Change (PGIC) is a validated instrument to gauge the patient's assessment of change in condition. This form will be completed by the patient at Visits 3, 4 and 5. The patient will answer a single question:

Since the start of the study Treatment Period, overall, my migraine condition is:

1 = Very much improved

2 = Much improved

3 = Minimally improved

4 = No change

5 = Minimally worse

6 = Much worse

7 = Very much worse

6.8.2 Hospital Anxiety and Depression Scale

The patient's total score on the Hospital Anxiety and Depression Scale (HADS) will be assessed at Visits 2, 3, 4, and 5. The HADS is a self-rated scale developed to assess psychological distress in non-psychiatric patients. It consists of 2 subscales, Anxiety and

Depression. The HADS aims to measure symptoms of anxiety and depression and consists of 14 items, 7 items for the anxiety subscale (HADS Anxiety) and 7 for the depression subscale (HADS Depression).

Note that the HADS is considered both an efficacy and safety endpoint.

6.8.3 Migraine Disability Assessment Questionnaire

The Migraine Disability Assessment Test (MIDAS) is a patient-reported test used to determine how severely migraines affect a patient's life. At Visits 2 and 5, patients are asked questions about the frequency and duration of their headaches, as well as how often these headaches limited their ability to participate in activities at work, at school, or at home.

The questionnaire contains 5 scored questions and 2 supplemental questions:

1. On how many days in the last 3 months did you miss work or school because of your headaches?

2. How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches? (do not include days you counted in question 1 where you missed work or school.)

3. On how many days in the last 3 months did you not do household work because of your headaches?

4. How many days in the last 3 months was your productivity in household work reduced by half or more because of your headaches? (do not include days you counted in question 3 where you did not do household work.)

5. On how many days in the last 3 months did you miss family, social or leisure activities because of your headaches?

A. On how many days in the last 3 months did you have any headache? (If a headache lasted more than one day, count each day)

B. On a scale of 0 - 10, on average how painful were these headaches? (where 0 = no pain at all, and 10 = pain which is as bad as it can be)

Only questions 1-5 contribute to the score of the assessment. The score obtained gives a measure of the extent of debilitation a patient’s migraines:

0 to 5, MIDAS Grade I, Little or no disability

6 to 10, MIDAS Grade II, Mild disability

11 to 20, MIDAS Grade III, Moderate disability

21+, MIDAS Grade IV, Severe disability

6.8.4 Migraine-Specific Quality of Life Questionnaire v2.1

At Visits 2, 3, 4, and 5, patients will be asked to complete the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ). The MSQ has been shown to have good psychometric performance in measuring headache impact in migraine patients. The MSQ is a 14-item patient-reported outcome instrument that measures the impact of migraine across 3 essential aspects of a patient's health-related quality of life over the past 4 weeks: role function-restrictive, role function-preventive, and emotional function. Patients respond to items using a 6-point scale: "none of the time," "a little bit of the time," "some of the time," "a good bit of the time," "most of the time," and "all of the time," which are assigned scores of 1 to 6, respectively. Raw dimension scores are computed as a sum of responses and rescaled from a 0 to 100 such that higher scores indicate better quality of life.

6.8.5 E-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.

On Visit 1, patients will be shown how to download the app to their iPhone or Android smartphone, will be provided with the credentials for opening the e-diary app, and assisted in entering the patient's specific typically used abortive medications for migraines. In addition, the site should set up the e-diary notifications for the patient within the IRT and the ePRO application.

On V2, V3, and V4, diary compliance should be reviewed, and patients should receive re-training as needed.

6.8.5.1 Screening/Wash-Out/Run-In Period

On a daily basis during the Screening/Wash-Out/Run-in and the Treatment phase, patients are to record in the e-diary information on presence of headache, duration of headache, headache characteristics and symptoms, peak pain severity, and use of any rescue (abortive) headache medication. Patients will complete the e-diary each morning for the previous day's headache assessment and rescue medication use. For evaluating randomization eligibility, the last 28 days of Run-In diary entries will be used, which includes diary entries logged on morning of the Baseline Visit.

6.8.5.2 Treatment Period

During the Treatment phase, patients will continue to record the data that was being collected during the Screening/Wash-Out/Run-In Period; however, they will also record study medication use for the expected morning and evening doses.

6.8.5.3 Diary Reminders and Site Responsibilities

Patients will receive daily reminders to complete their diary entries. Patients will receive a reminder to complete their diary if they miss two or more diary entries. Patients will also receive reminders twice a day to take their study drug.

Site staff will be alerted when diary entries are missed. If two days or more of e-diary entries are missed, the site should contact the patient for re-training and to instruct the patient on the importance of routine completion of their diary. 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 nonadherence be observed.

6.9 Safety Assessments

Safety will be assessed by evaluation of adverse events (AEs), vital signs, ECG, responses on the Columbia Suicide Severity Rating Scale, CSFQ-14, HADS, and by clinical laboratory and physical examination findings, including a nasal exam that includes visual inspection of the nasal passages.

6.9.1 Adverse Events Assessments

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

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

Additional information regarding definition and reporting requirements for AEs, serious AEs, and pregnancies is provided in Section 7.

6.9.2 Columbia- Suicide Severity Rating Scale

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 any method, 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 intervention as appropriate.

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 an increase in suicidal ideation or suicidal behavior, appropriate intervention should be prescribed.

6.9.3 Assessments of Changes in Sexual Function: Changes in Sexual Functioning Questionnaire Short-Form (CSFQ-14)

The Changes in Sexual Functioning Questionnaire Short-Form (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 12/EOT (Visit 5). It yields a total score, 3 subscales corresponding to phases of the sexual response cycle (i.e., desire, arousal, orgasm), and 5 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 2 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 to 5 = never). Items 10 and 14 are included in the total score but not in any scale score. Note: there is a male version and female version for the CSFQ-14.

Note that the CSFQ is considered both an efficacy and safety endpoint.

6.10 Optional Pharmacogenomics

For optional pharmacogenomic analyses, a blood sample will be obtained from each patient who provided separate written, signed informed consent for pharmacogenomic analysis.

These samples may be obtained at any post-screening visit, including an ET visit; however, it is preferred that they are collected at Baseline/Visit 2 whenever possible.

The purpose of this testing is to allow for whole genome sequencing and analysis for allelic polymorphisms related to treatment response to TNX-1900.

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

Unused extracted DNA may be stored up to 15 years and potentially utilized to develop a pharmacogenomic test for determining the likelihood of treatment response to TNX-1900.

A decision to not 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.

7 ADVERSE EVENTS

7.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation patient administered an IP that does not necessarily 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 related to the medicinal product, or not.

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition. Worsening of a pre-existing condition is considered an AE.

Events that occur in patients treated with placebo, or during treatment free periods of the study, are also considered AEs.

7.1.1 Unexpected Adverse Events

An expected AE is one for which the nature or severity is consistent with the known AE profile of the product. For a pre-approval test product, the known information is contained in the Investigator's Brochure (IB). For a marketed product, the known information is contained in the current package insert for the product.

An unexpected AE is one for which the nature or severity is not consistent with the applicable product information (e.g., IB for an unapproved IP or package insert/summary of product characteristics for an approved product). For example, hepatic necrosis would be unexpected (greater severity) if the IB only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral vasculitis would be unexpected (greater specificity) if the IB only listed cerebral vascular accidents.

Furthermore, reports that add significant information on specificity or severity of a known, already documented adverse reaction constitute unexpected events. Examples would be (a) acute renal failure as an expected adverse reaction with a subsequent new occurrence of interstitial nephritis (interstitial nephritis would be unexpected) and (b) hepatitis with a first occurrence of fulminant hepatitis (fulminant hepatitis would be unexpected.)

7.1.2 Treatment-Emergent Adverse Events

An AE is defined as treatment-emergent if the first onset or worsening is during or after the first administration of IP and not more than 30 days after the last administration of study drug.

7.1.3 Severity

7.1.3.1 Severity of Adverse Events

The clinical severity of an AE will be classified as:

Mild	Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the patient.
Severe	Interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity whereas an SAE is an AE that meets serious criteria, as described in Section 7.1.4.

7.1.3.2 Serious Adverse Events

7.1.4 Serious Adverse Events

A serious adverse event (SAE) is defined by federal regulation as any AE occurring at any dose that results in any of the following outcomes: death, life-threatening AE, hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in patient hospitalization, or the development of drug dependency or drug abuse.

Any SAE that occurs at any time during the study, including a clinically significant 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 period or the at-risk patient's treatment assignment or dosage.

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

- Results in death,

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

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

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 email 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] within 24 hours of the site's awareness of the SAE.

The investigator, or the sponsor or designee in the case of a central IRB, also must notify the ethics committee 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.

7.2 Adverse Event Assessment

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study patient presenting for medical care or upon review by a study monitor.

7.2.1 Performing Adverse Events Assessments

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE described previously. At each visit, the patient will be allowed time to spontaneously report any issues since the last visit or evaluation. The investigator will then monitor and/or ask about or evaluate AEs using nonleading questions, such as

"How are you feeling?"

"Have you experienced any issues since your last visit?"

"Have you taken any new medications since your last visit?"

Any clinically relevant observations made during the visit will also be considered AEs.

7.2.2 Reporting Serious Adverse Events

The investigator or designee must report all SAEs promptly to sponsor or designated CRO within 24 hours of first becoming aware of the event by completing, signing and dating the SAE Report Form, verifying the accuracy of the information recorded in the form with the source documents and eCRF, and sending the SAE form to the study CRO. SAEs should be sent to: [redacted] This written report should be submitted on the SAE form provided for this purpose. At the time of first notification, the investigator or designee should provide the following information, if available:

- Protocol number
- Reporter (study site and investigator)
- Patient's study number
- Patient's year of birth
- Patient's sex
- Date of first dose of IP(s)
- Date of last dose of IP(s), if applicable
- Adverse event term
- Date of occurrence of the event
- A brief description of the event, outcome to date, and any actions taken
- The seriousness criteria(on) that were met
- Concomitant medication at onset of the event
- Relevant medical history information
- Relevant laboratory test findings
- Investigator's opinion of the relationship to IP(s) ("Is there a reasonable possibility that the IP caused the SAE? Yes or No?")
- Whether and when the investigator was unblinded as to the patient's treatment assignment

Any missing or additional relevant follow-up information concerning the SAE should be sent to the sponsor/sponsor representative via the same contact details above as soon as possible on a follow-up SAE Report Form, together with the following minimal information (initial

report, AEs, date of occurrence, patient identification (ID), study ID, IP, and site number); this will allow the follow-up information to be linked to the initial SAE report.

Specific information may be requested by the study CRO using a follow-up request form or via email communication.

The investigator is required to comply with applicable regulations (including local laws and guidance) regarding the notification of his or her health authorities, Institutional Review Board (IRB), principal and coordinating investigators, study investigators, and institutions. Each investigator is obligated to learn about the reporting requirements for investigators in his/her country. The study monitor can assist with this.

7.2.3 Documentation of Adverse Events

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution or stabilization.

- AE name or term
- When the AE first occurred (start date and time)
- When the AE stopped (stop date and time or an indication of "ongoing")
- Severity of the AE
- Seriousness (hospitalization, death, etc.)
- Actions taken
- Outcome
- Investigator opinion regarding the AE relationship to the IP

The outcome at the time of last observation will be classified as:

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

- Unknown

*Fatal should only be selected as an outcome when the AE results in death. If more than one AE is judged to be possibly related to the patient's death, the outcome of death should be indicated for each such AE. Although "fatal" is usually an event outcome, events such as sudden death or unexplained death should be reported as SAEs.

7.2.4 Treatment of Adverse Events

AEs that occur during the study will be treated, if necessary, by established standards of care. If such treatment constitutes a deviation from the protocol, the decision about whether the patient may continue in the study will be made by the sponsor after consultation with the investigator and/or medical monitor.

If AEs occur in a patient that are not tolerable, the investigator must decide whether to stop the patient's involvement in the study and/or treat the patient. Special procedures may be recommended for the study drug, such as the collection of a serum sample for determining blood concentrations of study drug, specific tapering procedures, or treatment regimens, as appropriate.

For double-blinded studies, it is not necessary to unblind a patient's treatment assignment in most circumstances, even if an SAE has occurred. If unblinding is necessary, see Section 5.4 for a description of the unblinding procedures.

Action(s) taken may consist of:

IP interrupted	IP schedule was modified by temporarily terminating the prescribed regimen of IP.
IP withdrawn	IP schedule was modified through termination of IP.
Not applicable	Determination of a value is not relevant in the current context.
Unknown	Not known, not observed, not recorded, or refused.

7.2.5 Adverse Event Relationship

The investigator must assess each AE's relationship to the IP. The investigator must carefully consider possible when assigning a relationship of specific AEs to study drug. The categories for classifying the investigator's opinion of the relationship are as follows:

Not Related

This is an AE that is clearly not related to the study drug beyond a reasonable doubt. That is, another cause of the event is more 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 is an AE that could reasonably be considered caused by something else, and where there is no known or expected response pattern to the suspect 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.

7.2.6 Expectedness

An expected adverse drug reaction has a nature or severity that is consistent with the study intervention description as found in the Investigator Brochure (for unapproved investigational products). An adverse drug reaction is unexpected if it is not listed in the Investigator Brochure or is not listed at the specificity or severity that has been observed. Determination of expectedness is the responsibility of the sponsor and is necessary for determining if the event is a suspected unexpected serious adverse reaction which is reported to FDA and IRB in an expedited manner. The purpose of expedited reporting is to make regulators, investigators, and other appropriate personnel aware of new, important information on serious reactions. Such reporting will generally involve events previously unobserved or undocumented.

7.2.7 Clinical Significance

An abnormal laboratory value or test result, e.g., ECG, is clinically significant if the abnormality suggests a disease and/or there is organ toxicity that is new or worsened from Baseline.

7.2.8 Special Considerations

7.2.8.1 Adverse Events of Special Interest

Since IN administrations of agents can cause significant irritation of nasal mucosa, events of nasal irritation will be followed closely during the study and considered an AE of Special Interest. Investigators should monitor for tissue changes or lesions in the visualized nasal mucosa on nasal exam, and for pain or discomfort anywhere in the nasal cavity, sinuses or oropharynx.

Because intranasal administration of oxytocin can result in a transient, albeit short-lived and minor, rise in systemic oxytocin levels, there will be specific monitoring for the potential adverse effects of supraphysiological levels of oxytocin in plasma. It should, however, be noted that with intranasal administration and the proposed oxytocin dosing regimens, sustained and clinically relevant plasma oxytocin levels are not expected. It is out of an abundance of caution that close monitoring for potential safety signals will be carried out.

Theoretically, if substantial and sustained concentrations in plasma are achieved, plasma oxytocin may activate off target vasopressin receptors leading to antidiuretic effects. Thus, AEs that may involve changes in blood volume, blood pressure, and specific electrolyte disturbances (hyponatremia) will be AEs of special interest, e.g., new onset edema, hypervolemia, increased blood pressure, ECG changes related to cardiac hypertrophy or arrhythmia.

7.2.8.2 Pregnancy

All women of childbearing potential who participate in the study should be counseled on the need to practice adequate birth control and on the importance of avoiding pregnancy during study participation. Women should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected.

Pregnancy testing will be conducted prior to administration of the IP on every woman of childbearing potential. A woman who is found to be pregnant at the Screening Visit will be excluded from the study and considered to be a SF.

A woman who becomes pregnant during IP treatment or within 28 days of discontinuing the IP will be immediately discontinued from study participation. The investigator must report the pregnancy as if it were an SAE within 48 hours of learning of the pregnancy, to [redacted] using the Pregnancy Data Collection Form via the same fax number and/or email address as for SAE reporting. The investigator should contact the designated individual(s) who receive SAE notification and record information related to the pregnancy on a designated form provided by the sponsor or its designee.

Early Termination Visit assessments are required as soon as possible after learning of the pregnancy. The investigator is also responsible for following the pregnancy until delivery or termination. These findings must be reported on the designated form and forwarded to the designated individual(s). The event meets the SAE criterion only if it results in a spontaneous abortion after the first trimester or a congenital anomaly.

7.2.8.3 Overdosage

The maximal dose of study drug should not be exceeded during the study. Overdose that occurs during the study will be treated and documented as an AE/SAE if it fulfills the criteria. If the overdose does not result in an AE, it should be reported in written form to the designated individual(s) who receive SAE notification. The information contained therein should include study site identification, reporter identification, patient identification, IP, dose, action taken (e.g., supportive measures or therapy), and any comments.

As with any overdose, patients should be monitored closely and observed for expected and unexpected clinical and laboratory effects.

No specific antidote to oxytocin exists, so treatment should be directed at supportive care.

7.2.8.4 Abuse Potential

Although no indications of abuse have been reported, oxytocin will still be monitored for abuse or misuse.

8 STUDY ACTIVITIES

8.1 Screening Visit 1

Informed Consent

Before the potential participant 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.

After providing written informed consent, patients will be assessed for study entry eligibility.

Screening Assessments and Procedures:

1. Obtain written informed consent to participate
2. Inclusion/exclusion criteria
3. Demographics
4. Confirm chronic migraine diagnosis
5. Medical, neurological, and medication history
6. Physical examination
7. Nasal cavity examination
8. Vital signs
9. 12-lead ECG
10. Clinical laboratory tests (hematology, standard blood chemistry panel, TSH, HbA1C, and urinalysis)
11. Serum pregnancy test (for women of childbearing potential [WoCBP]) processed at central lab
12. Urine drug test
13. "Screening/Baseline" version of the C-SSRS. Any patient exhibiting Type 3, 4, or 5 suicidal ideation in the last 6 months or who has had suicidal behavior in the last 12 months should be deemed a screen failure and assessed for appropriate follow-up care. Results of the C-SSRS should be reviewed to ensure the patient is not experiencing suicidal ideation or has had suicidal behavior that requires emergency intervention
14. MSI-BPD
15. Placebo response training

16. Provide the patient with the e-diary training. Reminder notifications for diary completion should be set up in the IRT and in the ePRO app according to the patient's preferences

During this Screening/Wash-Out/Run-In Period, if any test results come back and indicate a patient's ineligibility for the study, the patient should be considered a screen-failure (SF) and informed that they are not eligible for the study and can stop completing the e-diary. However, if the investigator determines that the patient should be brought back into the clinic for re-testing, the patient should continue completing the e-diary until a final determination regarding eligibility is made.

In addition, any patients not meeting the randomization criteria will be considered a SF.

Only those patients meeting all the inclusion and none of the exclusion criteria will be eligible to continue.

8.2 Baseline/Randomization Visit 2 (Day 1)

If the patient meets randomization (randomization will be stratified by study site and concomitant migraine preventive medication) 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 an SF, with the reason documented. There is no requirement for a follow-up visit for SFs; however, the investigator should advise patients who have washed off of medications for the study on next steps of treatment.

If the patient meets randomization criteria, the following procedures will be completed at V2:

- Eligible patients will be randomized in a 1:1:1 ratio to one of 3 treatment arms (A, B or C) as summarized in Section 5.2. Randomization will be stratified by study site and concomitant migraine preventive medication.
- The patient should also be provided with the opportunity to sign a separate consent form for the optional pharmacogenomics blood draw and analysis. Participation in this optional portion of the study is not required. Ideally, the blood drawn for the optional pharmacogenomics should be drawn at the Baseline visit; however, it can be drawn at a subsequent visit if needed. A patient can decide to decline the optional pharmacogenomics but still participate in the main study.

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

- Confirm patient's eligibility.
- Review completed diary data with the patient. Provide re-training.

- Update medical history (if any new information has been provided since the Screening Visit).
- Assess occurrence of AEs.
- Assess changes in medication history and concomitant medications.
- Conduct a physical examination, including vital signs and weight.
- Conduct a nasal cavity examination.
- Conduct a 12-lead ECG
- Obtain clinical laboratory tests (standard blood chemistry panel and urinalysis)
- Perform urine pregnancy test (for WoCBP)
- Obtain blood sample for optional pharmacogenomics (after the separate ICF has been signed for pharmacogenomic substudy) - if not drawn at a prior visit
- 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. Results of the C-SSRS should be reviewed to ensure the patient is not experiencing suicidal ideation or has had suicidal behavior that requires emergency intervention.
- Have the patient complete placebo response training.
- Administer the HADS: Hospital Anxiety and Depression Scale
- Have the patients complete the following rating scales:
    1. MIDAS: Migraine Disability Assessment questionnaire
    2. MSQ: Migraine-Specific Quality of Life Questionnaire v2.1
    3. CSFQ-14: Changes in Sexual Functioning Questionnaire Short-Form
- Verify patient's ability to use an intranasal device prior to leaving the clinic at Baseline/Randomization/Visit 2. Patient will also take their first study drug dose before leaving the clinic.
- Once it has been confirmed that the patient remains eligible, randomize patient via interactive response technology (IRT) Randomization System
- Dispense 2 unopened nasal applicators of double-blind study drug as assigned via the IRT (one is marked "MORNING" and the other is marked "EVENING"). Prime the two study drug bottles. Supervise the patient as they take one dose of study drug from the appropriate study drug bottle (AM or PM) depending on appointment time.
- Each treatment bottle number should be recorded in the patient's records. Review patient instructions regarding study drug dosing and diary completion

8.3 Visits 3 (Week 4) and 4 (Week 8)

Visits 3 and 4 are similar study visits that are scheduled to be conducted after 4 weeks, and 8 weeks of treatment, respectively. The following assessments and procedures are scheduled for both of these visits in the following general order:

- Assess changes in medication history and concomitant medications
- Assess occurrence of AEs
- Conduct nasal exam cavity examination
- Obtain vital signs
- Conduct a12-Lead ECG
- Obtain clinical laboratory tests (standard blood chemistry panel and urinalysis)
- Perform urine pregnancy test (for WoCBP).
- Obtain blood sample for optional pharmacogenomics (after the separate ICF has been signed for pharmacogenomic substudy) - if not drawn already at a prior visit
- Have the patient complete placebo response training.
- Administer the "Since Last Visit" version of the C-SSRS. Results of the C-SSRS should be reviewed to ensure the patient is not experiencing suicidal ideation or has had suicidal behavior that requires emergency intervention
- Have the patient complete:
    1. PGIC: Patient Global Impression of Change
    2. HADS: Hospital Anxiety and Depression Scale
    3. MSQ: Migraine-Specific Quality of Life Questionnaire v2.1
- Review completed diary data and diary compliance with the patient. Provide re-training.
- Assess study drug compliance and collect previously dispensed study drug and bottles
- Dispense 2 unopened nasal applicators of double-blind study drug as assigned via the IRT (one is marked "MORNING" and the other is marked "EVENING"). Prime the two study drug bottles.
- After all 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.

8.4 Visit 5 (Week 12) or Early Termination Visit

Visit 5 should occur after 12 weeks of double-blind study drug treatment. At this visit, the patient will return all study drug. The following assessments are completed:

- Assess changes in medication history and concomitant medications
- Assess occurrence of AEs
- Conduct a physical examination, including vital signs, weight
- Conduct a nasal cavity examination
- Conduct a 12-lead ECG
- Obtain blood for clinical laboratory tests (hematology, standard blood chemistry panel, urinalysis)
- Perform in-clinic urine pregnancy test (for WoCBP)
- Obtain blood sample for optional pharmacogenomics (after the separate ICF has been signed for pharmacogenomic substudy) - if not drawn at a prior visit
- Have the patient complete placebo response training
- Administer the "Since Last Visit" version of the C-SSRS. Results of the C-SSRS should be reviewed to ensure the patient is not experiencing suicidal ideation or has had suicidal behavior that requires emergency intervention
- Have the patient complete:
    1. PGIC: Patient Global Impression of Change
    2. HADS: Hospital Anxiety and Depression Scale
    3. MIDAS: Migraine Disability Assessment questionnaire
    4. MSQ: Migraine-Specific Quality of Life Questionnaire v2.1
    5. CSFQ-14: Changes in Sexual Functioning Questionnaire Short-Form
- Review completed diary data and diary compliance with the patient. Provide re-training as needed.
- Assess study drug compliance and collect previously dispensed study drug and bottles
- After all the assessments at each visit have been completed, the patient should be given an appointment to return to the clinic for the Follow-up visit.

All patients who withdraw early from the study will be encouraged to complete the ET Visit for safety evaluations (Visit 5) within 7 days from withdrawal of study, followed by a Safety Follow-up Visit (Visit 6) approximately 14 days from the last study drug administration.

8.5 Visit 6 (Week 14)/Safety Follow-up

Visit 6 (Week 14) or Safety Follow-up in-person visit will occur 14 days after the final treatment (Visit 5).

The following assessments are completed:

- Assess AEs
- Conduct nasal exam, only if there is any ongoing or new AE of the nasal cavity
- Conduct vital signs
- Obtain samples for clinical lab tests (hematology, blood chemistry, and/or urinalysis), only if there are any clinically significant findings from the V5 labs
- Perform in-clinic urine pregnancy test (for WoCBP)
- Optional blood draw for pharmacogenomics (after the separate ICF has been signed for pharmacogenomic substudy) - if not drawn at a prior visit
- Administer the “Since Last Visit” version of the C-SSRS. Results of the C-SSRS should be reviewed to ensure the patient is not experiencing suicidal ideation or has had suicidal behavior that requires emergency intervention

8.6 Early Termination (After Randomization)

In accordance with the Declaration of Helsinki, patients have the right to withdraw from the study at any time for any reason, and they will be advised of this right. The investigator and Tonix also have the right to remove patients from the study. Specific reasons for removal of a patient from the study could include, but are not limited to:

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

Patients who wish to terminate their participation in the study should be instructed to come to the clinic for an ET Visit. The purpose of the ET Visit is to obtain critical information about the patient’s participation and should be scheduled preferably before there has been a substantial lapse in study drug usage. However, even if there has been a drug lapse, the

patient should be encouraged to return to the clinic for this visit and should be instructed to return all study drug and bottles. Additionally, the patient should be encouraged to also subsequently attend the Safety Follow-Up Visit (Visit 6). 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.

In addition to documenting the reason for ET during the ET visit, assessments and procedures should be completed according to the V5 schedule. For the Safety Follow-Up Visit (Visit 6), assessments and procedures should be completed according to the V6 schedule.

9 QUALITY CONTROL AND ASSURANCE

Unless otherwise specified, procedures, data collection and evaluation will be conducted as per the standard operating procedures of the CRO. The investigator will assume the responsibility of ensuring the completeness and accuracy of the clinical data. All data will be verified for quality control and will also be patient to audits from Tonix or designee to ensure quality.

10 PLANNED STATISTICAL METHODS

10.1 General Considerations

All safety and efficacy data will be listed and summarized. Unless otherwise specified, Baseline is defined as the last observed measurement, whether scheduled or unscheduled, prior to study drug administration. Safety and efficacy endpoints will be summarized by treatment group. Continuous variables will be summarized using the number of patients with data (n), mean, SD, median, minimum, and maximum. Selected continuous variable summaries will also include the standard error. Categorical variables will be summarized using frequency counts and percentages. All values summarized will also be presented in listings.

The statistical analysis plan (SAP) will provide further details for statistical methodology.

All analyses will be performed using SAS® version 9.4 or higher, unless otherwise specified.

10.1.1 Estimand

The primary efficacy endpoint is defined as the change in monthly migraine days from Baseline (last 28 days prior to randomization) to month 3 (last 28 days of treatment). For defining months, diary days will be divided into 28 day "months"; Days 1 to 28 will be Month 1; Days 29 to 56 will be Month 2; and Days 57 to 84 will be Month 3. The change in count of days with migraine vs the baseline will be compared between treatment groups.

The target population is all patients in the mITT population with CMs as defined by the inclusion/exclusion criteria.

A "while on treatment" policy strategy will be used for all intercurrent events. That is, the data will be considered independently from any intercurrent event, such as rescue medication usage and study discontinuation. The approach for partial and missing data is described in Section 10.1.3.

The population-level summary will be the model-based least-squared means for each arm and differences between treatment arms (analyzed as randomized) at month 3.

10.1.2 Multiple Comparisons

A multiplicity algorithm will maintain an overall alpha level of 0.05 across the two dose groups as well as the primary endpoint of change in monthly migraine days from Baseline to month 3, using the graphical method. Full details will be specified in the SAP.

10.1.3 Missing Data

Every effort will be made to retain patients in the study; however, patients are free to withdraw from the study at any time for any reason. Patients that withdrawal early will be

asked to return to the clinic for an Early Termination Visit for completion of assessments (see Schedule of Assessments

).

The monthly migraine count will be calculated for patients that have at least 14 days of non--missing data for a given month. For patients with less than 28 days of data, the counts will be normalized to 28 days by taking 28* [migraine count] / [days of non-missing data].

If less than 14 days are available for a month, then the month will remain missing, but the patient's other months will contribute to the estimation via a mixed-effects model of repeated measures. The mixed model repeated measures analysis will provide unbiased estimates under the assumption that data are missing at random (MAR). Sensitivity analyses will confirm the robustness of the results to deviations from this assumption.

For responder analyses using the monthly migraine days, the values as imputed above will be utilized. If a month is missing, then the patient will be considered a non-responder for that month.

For other responder analyses, patients with missing values will be treated as non-responders.

10.2 Determination of Sample Size

The planned total number of randomized patients is approximately 300 and will be randomized 1:1:1 to TNX-1900 30 IU QAM, placebo QPM: TNX-1900 30 IU BID: or placebo BID. The sample size estimate was derived using a two-sided t-test with 90% power and 5% two-sided significance level to test the primary efficacy statistical superiority hypothesis of TNX-1900 30 IU BID over placebo.

Based on a post-hoc analysis of a chronic migraine subgroup from a prior study, it is anticipated that a difference in mean change from Baseline to study end (last 28 days of double-blind) in migraine headache days between TNX-1900 30 IU BID and placebo BID would be approximately 1.84 with a common standard deviation of ± 3.95. As such the required sample size per group is approximately 100.

Accounting for the multiplicity adjustment by applying an alpha of 2.5% to the first test yields power of approximately 85% with the above assumptions.

10.3 Analysis Populations

The following populations will be utilized for the analyses of data. Disposition of patients will use the All Patients Population. The safety analyses will be conducted on the Safety Population. The modified intent-to-treat (mITT) Population will be used for the primary efficacy analyses.

10.3.1 All Patients Population

This includes all patients available in the electronic data capture system; patients will be presented by their randomized treatments (if applicable).

10.3.2 Modified Intent-to-Treat Population

The mITT population will include all randomized patients who received at least one dose of study drug and had at least one post-Baseline evaluable month (that is, at least one of the three 28-day periods had at least 14 non-missing e-diary entries; see full details in SAP). This population will be used to summarize the primary and other efficacy data. Patients will be analyzed according to randomized treatment assignment.

10.3.3 Safety Population

The Safety Population will include all patients who received at least one dose of study drug. This population will be used to summarize the safety data. Patients will be analyzed according to their treatment received; if an error in issuing IP occurs and a patient receives a mix of treatments, they will be analyzed under the treatment arm with the most IP issued to the patient.

10.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics such as age, gender, race/ethnicity, height, weight, BMI, family status, education, employment status, smoking history, use of preventative migraine medications, and Migraine Diagnostic criteria will be summarized by treatment group (TNX-1900 and placebo) and overall using descriptive statistics.

Medical History will be coded using the most current version Medical Dictionary for Regulatory Activities (MedDRA)® and summarized by System Organ Class and Preferred Term using frequency counts by treatment group.

10.5 Primary Endpoint(s)

10.5.1 Primary Safety Endpoint(s)

Incidence of AEs, and changes in C-SSRS scores, HADS scores, physical examination and vital sign findings, clinical laboratory values, ECG parameters, and CSFQ-14 scores.

10.5.2 Primary Efficacy Endpoint(s)

Mean change in the number of monthly migraine headache days from the last 28 days of Baseline to the last 28 days of treatment (i.e., month 3). A migraine headache day is any calendar day (0:00 to 23:59) in which the patient records in the e-diary:

- An attack lasting 4 hours or more and meeting the ICHD-3 criteria for migraine without aura (Appendix A), or

- A migraine with aura, or
- An attack that meets ICHD-3 criteria for probable migraine, (a migraine subtype fulfilling all but one criterion (B-D) for migraine without aura), or
- An attack of any duration that was believed by the patient to be a migraine and was relieved by a triptan, ergot derivative, or other migraine-specific abortive medication.

10.6 Secondary Endpoint(s)

10.6.1 Key Secondary Efficacy Endpoint(s)

- Proportion of patients experiencing a ≥ 50% reduction in the number of migraine headache days from the last 28 days of Baseline to the last 28 days of treatment in each treatment group.
- Mean change in the number of days using rescue medication (triptan, ergot derivative, or other migraine-specific acute medication) from the last 28 days of Baseline to the last 28 days of treatment in each treatment group.
- Proportion of patients with a PGIC rating of 1, "very much improved", or 2, "much improved", at Week 12.
- Mean change in the number of moderate or severe headache days from the last 28 days of Baseline to the last 28 days of treatment in each treatment group. A moderate or severe headache day is defined as any calendar day wherein a patient records a headache or migraine of moderate or severe peak intensity in the e-diary.
- Mean change in the number of migraine headache days from the last 28 days of Baseline to average number per 28 days over the entire 12-week duration of Treatment Period.
- Mean change from Baseline in the Migraine-Specific Quality of Life Questionnaire (MSQ v2.1) at Week 12

10.6.2 Secondary Efficacy Endpoint(s)

- Mean change from Baseline in the MIDAS Test total score at Week 12.
- Mean change from Baseline in the HADS at Week 12.
- Mean change from Baseline in patient-rated Changes in Sexual Functioning Questionnaire Short-Form (CSFQ-14) total score in males and in females, analyzed separately, at Week 12.

10.6.3 Exploratory Endpoint(s)

- Proportion of patients experiencing a ≥ 75% reduction in the number of migraine headache days from the last 28 days of Baseline to the last 28 days of treatment in each treatment group.
- Proportion of patients with fewer than 14 headache days or fewer than 8 migraine headache days per 4 weeks over the 12-week period.
- Mean change from Baseline in number of headache free days from the last 28 days of Baseline to the last 28 days of treatment.
- PGIC rating (1-7) at Week 12

10.7 Analysis Methods

10.7.1 Disposition and Demographics

The number and percentage of patients in each analysis population will be summarized. The number of patients screened, patients enrolled, and the number and percentage of patients completing the study, discontinuing from the study and reasons for discontinuation will also be reported. All percentages will be calculated using the number of patients enrolled as the denominator.

Demographics and baseline characteristics will be reported for the efficacy and safety populations. Categorical items will be reported with counts and percentages; continuous items will be reported using summary statistics (mean, SD, median, minimum, maximum).

10.7.2 Efficacy Analysis

10.7.2.1 Primary Efficacy Analysis

Summary statistics (mean, SD, median, minimum, maximum) for the primary efficacy endpoint will be reported for the change from the Baseline to month 3 for each of the treatment groups. The change from Baseline will be analyzed in a Mixed-Effects Model of Repeated Measures (MMRM) model with fixed effects of treatment, month, baseline value, treatment by month interaction, baseline by month interaction, site, and stratification factor (preventive medication use); an unstructured covariance matrix will be used. Least square means (LSMs), standard errors, and the LSM differences (each treatment vs placebo) will be reported for each month. Denominator degrees of freedom will use the Kenward Rogers approach. Should the model fail to converge, heterogeneous Toeplitz, heterogeneous first-order autoregressive, Toeplitz, first order autoregressive and compound symmetric will be attempted in that order; in these cases, the sandwich estimator (Diggle and Kenward 1994) will be used to estimate the standard errors of the fixed effects parameters and the denominator degrees of freedom will utilize the DDFM=BETWITHIN option in SAS®.

To account for the blinded interim sample size re-estimation (Section 10.8), data from the interim and post-interim cohorts will be combined using the inverse normal method to test

the null hypotheses that there is no difference in the change from Baseline to month 3 in number of migraine days per month between each of the active groups and placebo (Cui et al 1999):

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

Where:

Z_1 = the Z statistic for the first stage
Z_2 = the combination test statistic at the end of the second stage
w_i = the weighting applied for each associated Z statistic
p_1 = the first stage p-value
p_2 =the second stage p-value based on second stage participants

The weights are defined prospectively according to the square-root of the planned proportion of participants in the two stages, relative to the preplanned total enrollment of 300 participants, as $w_i = \sqrt{0.5}$. In order to control the type-I error, adaptive changes of the stage wise sample sizes will not lead to changes of the weights (Lehmacher and Wassmer 1999).

For each difference of interest, the combined point estimate of the difference, and adjusted 95% confidence interval will be provided (Lawrence and Hung 2003). The formulas for the inferential statistics are given below.

The combined point estimate of the treatment difference is provided in formula (2) and its adjusted confidence interval is provided in formula (3).

$$\hat{\delta} = \frac{r_1 \hat{\delta}^{(1)} + \sqrt{1-r_1}\sqrt{N^* - r_1}\,\hat{\delta}^{(2)}}{r_1 + \sqrt{1-r_1}\sqrt{N^* - r_1}} \quad (2)$$

$$\hat{\delta} \pm \left(\left| \frac{\hat{\delta}}{Z_2} \right| z_{\alpha/2} \right) \quad (3)$$

Where:

$\hat{\delta}^{(1)}$: LS Means difference from stage 1 analysis (interim cohort analysis)

$\hat{\delta}^{(2)}$: LS Means difference from stage 2 analysis (post-interim cohort analysis)

r_1: total number of patients planned to be included at the interim analysis divided by the total number of patients originally planned (planned sample size), i.e., 0.5

N^*: final total number of patients divided by the total number of patients originally planned

Z_2: combination test statistic at the end of the second stage obtained in equation 1

10.7.2.2 Sensitivity Analyses

Three sensitivity analyses will be performed:

- Multiple imputation methodology will be utilized to impute complete datasets with three monthly observations for all patients in the mITT population. This will be done within each treatment group conditioned on each patient's non-missing data (including baseline), site, and the stratification factor.

- A tipping point analysis will be performed using the above MI datasets and applying an increasing penalty to the active group until statistical significance is no longer achieved.

- Finally, a missing-not-at-random multiple imputation approach will be utilized taking into account the reason for discontinuation; intermittent missing data will still be assumed to be missing at random.

Full details of each analysis will be provided in the SAP.

10.7.2.3 Secondary Analyses

Continuous endpoints will be analyzed in a manner parallel to the primary analysis. Daily diary measures will be aggregated to monthly values and analyzed in the MMRM. Visit-based measures will use visit in place of month in the MMRM.

For binary endpoints, the counts and percentages of responders in each treatment arm will be reported as well as the 95% CIs of those percentages. Patients with missing data will be considered non-responders. The difference in percentages in the active and placebo arms will be reported along with its 95% CI based on the Sato variance estimator. Pairwise p-values will compare each treatment arm to placebo based on a Cochran-Mantel-Haenszel (CMH) stratified by preventive medication use.

Full details of the secondary analyses will be provided in the SAP.

10.7.3 Safety Analysis

All safety analyses will be completed for the Safety Population. All safety data will be tabulated and listed. No formal statistics will be performed for the safety analysis.

Adverse events that occur between the time written informed consent is provided and the start of study drug administration will be considered pretreatment AEs. Adverse events that start during or after study drug administration, or AEs with an onset prior to study drug administration that worsen after study drug administration will be considered TEAEs. All AEs will be coded using MedDRA, and the incidence of TEAEs will be summarized overall and by preferred term and system organ class for each treatment group. Incidence of TEAEs will also be summarized by severity and relationship to study drug. Serious AEs, TEAEs involving the nasal passages, and TEAEs leading to discontinuation of study drug will also be summarized.

Actual values and changes from Baseline for clinical laboratory test results, ECG parameters, vital signs, HADS scores, and CSFQ-14 scores will be summarized by treatment group and

visit 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, based on the C-SSRS, will be summarized by treatment group. For each laboratory test, individual patient values will be listed and values outside of the standard reference range will be flagged.

10.8 Interim Analysis

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 end of the Treatment Period is above a pre-specified threshold; or to stop the study early for futility if the conditional power is sufficiently low. The conditional power will be calculated based on the first cohort, using the following formula (Mehta and Pocock 2010):

$$CP(Z_1,\check{n}_2) = 1 - \Phi\left(\frac{Z_\alpha\sqrt{n_2} - Z_1\sqrt{n_1}}{\sqrt{\check{n}_2}} - \frac{Z_1\sqrt{\check{n}_2}}{\sqrt{n_1}}\right)$$

Where:

Z_1 is the value of the Z score at the interim
n_1 is the actual sample size at the interim
n_2 is the total planned sample size
$\check{n}_2$ is the total planned sample size minus the actual sample size at the interim

The study team will only be informed of the non-binding recommendation to maintain the original sample size, increase the sample size (by a fixed, pre-specified amount), or discontinue the study for futility.

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

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Institutional Review Board or Ethics Committee Approval

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.

11.2 Ethical Conduct of the Study

This protocol is written in accordance with the principles established by the 18th World Medical Assembly General Assembly (HelsinkiDeclaration, 2014) 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.

11.3 Patient Information and 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. The patient should also be asked in the informed consent form (ICF) for permission for the principal investigator or his designee to contact the patient's other personal physicians, as appropriate, concerning participation in the study.

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

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

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

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

11.4 Patient Confidentiality

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 or initials, nor by their date of birth (DOB), but rather by their assigned study identification numbers. The investigator should keep a separate record of the patient initials, DOB, randomization codes, patient names, address, and contact information. Documents that contain the names or initials or DOBs associated with these 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.

11.5 Study Monitoring

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 email, 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 all questions raised, and difficulties detected by the monitor.

11.6 Case Report Forms and Study Records

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.

11.7 Protocol Violations/Deviations

No protocol waivers will be allowed.

A protocol deviation is any noncompliance with the clinical trial protocol or ICH GCP requirements. The noncompliance may be either on the part of the patient, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 3 working days of identification of the protocol deviation, or within 3 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to the sponsor's designated CRO Protocol deviations must be sent to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the protocol deviation guidance plan.

11.8 Access to Source Documentation

All documentation and material provided by Tonix for this study are to be retained in a secure location and treated as confidential material.

Information recorded in the electronic data capture system should be supported by corresponding source documentation. Examples of acceptable source documentation include,

but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

11.9 Data Management

Tonix or designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and [redacted] standard operating procedures. A comprehensive data management plan (DMP) will be developed, including a data management overview, description of database contents, annotated CRF, pre-entry review list, self-evident correction conventions, query contacts, and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries will be described in the DMP.

11.9.1 Quality Assurance/Audit

This study will be patient to audit by Tonix or its designee. Audits may be performed to check compliance with GCP guidelines and can include:

- Site audits
- Trial Master File audits
- Database audits
- Document audits (e.g., Clinical Study Protocol and/or Clinical Study Report)

Tonix or its designee may conduct additional audits on a selection of study sites, requiring access to patient notes, study documentation, and facilities or laboratories used for the study.

The study site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB or regulatory authorities according to GCP guidelines. The investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with CRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the investigator that it intends to conduct an inspection, the investigator shall notify Tonix immediately.

11.10 Retention of Data

The investigator shall retain and preserve 1 copy of all data generated during the study, specifically including, but not limited to, those defined by GCP as essential until:

- At least 2 years after the last marketing authorization for the IP has been approved or the sponsor has discontinued its research with the IP, or
- At least 2 years have elapsed since the formal discontinuation of clinical development of the IP.

These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor has 30 days to respond to the investigator's notice, and the sponsor has further opportunity to retain such materials at the sponsor's expense.

11.11 Financial Disclosure

Trial TNX-OX-CM201 is funded in whole by the sponsor, Tonix Pharmaceuticals, Inc. Sites/institutions must ensure that investigators and all sub-investigators submit a completed financial disclosure form accompanied with a Form FDA 3454 or 3455, as applicable, prior to trial initiation, or as otherwise required in accordance with applicable law.

11.12 Publication and Disclosure Policy

No presentations, abstracts (including meeting abstracts), or other publications based on the conduct or results of this study will be permitted without the express written permission of Tonix or its designated agent. All such presentations or publications will proceed only as collaborations between Tonix and the investigators. If the investigator wishes to publish the results of this study, a copy of the proposed manuscript or abstract (including meeting abstracts) will be provided to Tonix or its designee for review, revision, and approval at least 60 days before the expected date of submission for publication, unless otherwise arranged with Tonix in writing. This will enable Tonix to protect its proprietary information and augment the publication with insights or information of which the investigator may not be aware. Patient names and other identifiers, such as photographs or audio or video recordings, may not be disclosed in any publication or public forum without prior written authorization from the patients involved or their legal guardians.

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APPENDIX A. ICHD-3 DIAGNOSTIC CRITERIA

1.1 Migraine without Aura

A. At least 5 attacks fulfilling criteria B through D

B. Headache attacks lasting 4 to 72 hours (untreated or unsuccessfully treated)

C. Headache has at least 2 of the following 4 characteristics:

1. unilateral location
2. pulsating quality
3. moderate or severe pain intensity
4. aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)

D. During headache at least 1 of the following:

1. nausea and/or vomiting
2. photophobia and phonophobia

E. Not better accounted for by another ICHD-3 diagnosis

1.2 Migraine with Aura

A. At least 2 attacks fulfilling criteria B and C

B. One or more of the following fully reversible aura symptoms:

1. visual
2. sensory
3. speech and/or language
4. motor
5. brainstem
6. retinal

C. At least 3 of the following 6 characteristics:

1. at least one aura symptom spreads gradually over ≥5 minutes
2. two or more aura symptoms occur in succession

3. each individual aura symptom lasts 5 to 60 minutes

4. at least one aura symptom is unilateral

5. at least one aura symptom is positive

6. the aura is accompanied, or followed within 60 minutes, by headache

D. Not better accounted for by another ICHD-3 diagnosis

1.3 Chronic Migraine

A. Headache (migraine-like tension-type-like) on ≥15 days/month for >3 months, and fulfilling criteria B and C

B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for 1.1 *Migraine without aura* and/or criteria B and C for 1.2 *Migraine with aura*

C. On ≥8 days/month for >3 months, fulfilling any of the following:

1. criteria C and D for 1.1 *Migraine without aura*

2. criteria B and C for 1.2 *Migraine with aura*

3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

D. Not better accounted for by another ICHD-3 diagnosis