STATISTICAL ANALYSIS PLAN

STUDY 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

SHORT TITLE:	PREVENTION
NCT#:	NCT05679908
CLIENT:	Tonix Pharmaceuticals
IND NUMBER(S):	[redacted]
PREPARED BY:	[redacted]

[redacted]

ACKNOWLEDGEMENT AND SIGNATURE SHEET

VERSION HISTORY

[redacted]

[redacted]

TABLE OF CONTENTS

[redacted]

[redacted]

[redacted]

LIST OF TABLES

LIST OF FIGURES

[redacted]

1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
BID	twice daily
BMI	body mass index
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
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
ECG	electrocardiogram
EMA	European Medicines Agency
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
ICHD-3	International Classification of Headache Disorders, 3rd edition
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND	Investigational New Drug
IRB	Institutional Review Board
IP	Investigational product
IU	international unit
IWRS	interactive web response system
LOE	lack of efficacy
LS, LSM	least square, least square means
mITT	modified intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities

[redacted]

Abbreviation	Term
MAR	missing at random
MCMC	Markov Chain Monte Carlo
MI	multiple imputation
MIDAS	Migraine Disability Assessment questionnaire
MMRM	Mixed-Effects Model of Repeated Measures
MSI-BPD	McLean Screening Instrument for Borderline Personality Disorder
MSQ	Migraine-Specific Quality of Life Questionnaire
NDA	New Drug Application
NSAIDs	Non-steroidal anti-inflammatory drugs
PGI-C	Patient Global Impression of Change
QAM	Every morning
QPM	Every evening
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SF	screen failure
SOC	system organ class
TEAE	Treatment-Emergent Adverse Event
US	United States
WHO-DD	World Health Organization Drug Dictionary

2. PURPOSE OF THE ANALYSES

This statistical analysis plan (SAP) describes the planned analysis and reporting for Protocol TNX-OX-CM201 (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).

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials. All work planned and reported for this SAP will follow internationally accepted guidelines for statistical practice, as published by the American Statistical Association and the Royal Statistical Society.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc, or unplanned exploratory analysis performed will be clearly identified as such in the final CSR.

[redacted]

- [redacted]
- [redacted]
- [redacted]

The reader of this SAP is encouraged to also read the clinical protocol, and other identified documents, for details on the planned conduct of this study. Operational aspects relating to collection and timing of planned clinical assessments are not repeated in this SAP unless they are relevant to the planned analysis.

[redacted]

3. PROTOCOL SUMMARY

This is a double-blind, randomized, placebo-controlled, multicenter, 3 arm Phase 2 study. Men and women with a current diagnosis of chronic migraine (CM) according to the International Classification of Headache Disorders, 3rd edition (ICHD-3) and who meet the criteria for the study at Screening will enter a Run-in Period 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 preventive vs. no preventive). All participants will administer study drug twice a day, mornings and evenings, in a double-blind design.

The study will be conducted in 3 periods (Screening/Washout/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 (Visit 1: Screening Visit)

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. 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.

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 (up to one is allowed). 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.

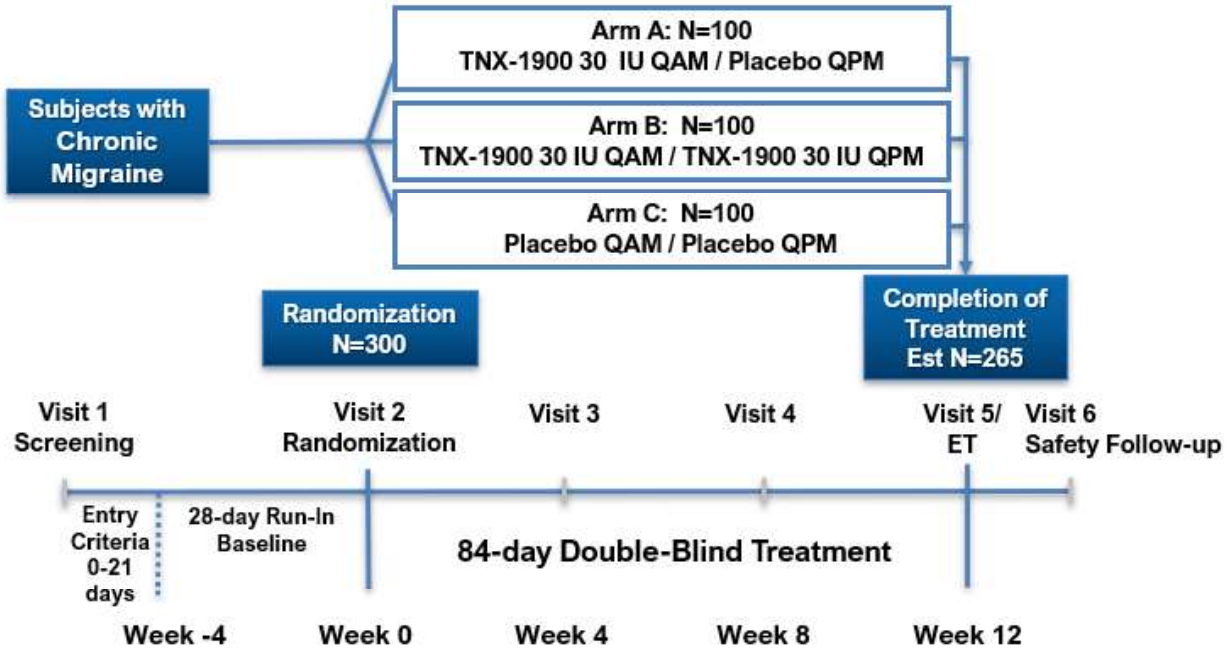
All patients who withdraw early from the study will be encouraged to complete an Early Termination Visit for safety evaluations (Visit 5 [V5]) within 7 days of withdrawal from the study. Study end is after Visit 5/ET. A Safety Follow-up Visit (Visit 6 [V6]) will occur 14 days after V5/ET.

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



[redacted]

4. ANALYSIS SAMPLES

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.

4.1. All Patients Population

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

4.2. 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 has at least 14 non-missing e-diary entries; see Section 9.1.1). This population will be used to summarize the primary and other efficacy data. Patients will be analyzed according to randomized treatment assignment.

4.3. 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 investigational product (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.

5. ESTIMANDS FOR PRIMARY AND KEY SECONDARY EFFICACY ENDPOINTS

5.1. Primary Efficacy

The primary efficacy endpoint is defined as the mean 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 CM as defined by the inclusion/exclusion criteria.

In general, 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. One exception is that patients that report a headache believed to be a migraine that was resolved by a migraine-specific abortive rescue medication will be counted as a migraine (see section 9.1).The approach for partial and missing data is described in Section 9.1.1.

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. The model is given in Section 9.1.2.

5.2. Key Secondary Efficacy

There are six key secondary efficacy endpoints. For all, the target population is all patients in the mITT population with CMs as defined by the inclusion/exclusion criteria. The key secondaries (in order) are:

- Proportion of patients experiencing a ≥ 50% reduction in the number of migraine headache days from the last 28 days of Baseline to the month 3 28-day normalized migraine headache days. The percent change from baseline will be calculated for each month as 100*[monthly count– baseline count] / [baseline count].
    - A composite strategy will be employed to handle missing data and discontinuation. Concomitant medications and all other intercurrent events will use a treatment policy strategy; data will be analyzed as observed. For all missing data (whether or not due to discontinuation), they will be assumed to be non-responders; that is, failure to stay on-trial and provide data is assumed to reflect non-response to study treatment.
    - The population-level summary will be the percentages of responders in each arm and difference in percentages of responders between treatment arms (analyzed as randomized) at month 3. See Section 9.1.4.2 for full details

- 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.
    - 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 study discontinuation. The approach for partial and missing data is described in Section 9.1.1 (Missing data approach will be identical to that of the primary endpoint).
    - 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. See Section 9.2.1.1 for details.
- Proportion of patients with a Patient Global Impression of Change (PGIC) rating of 1, "very much improved", or 2, "much improved", at Week 12.
    - A composite strategy will be employed to handle missing data and discontinuation. Concomitant medications and all other intercurrent events will use a treatment policy strategy; data will be analyzed as observed. For all missing data (whether or not due to discontinuation), they will be assumed to be non-responders; that is, failure to stay on-trial and provide data is assumed to reflect non-response to study treatment.
    - The population-level summary will be the percentages of responders in each arm and difference in percentages of responders between treatment arms (analyzed as randomized) at month 3. See Section 9.2.1.2 for full details
- 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.
    - 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 study discontinuation. The approach for partial and missing data is described in Section 9.1.1 (Missing data approach will be identical to that of the primary endpoint).
    - 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. See Section 9.2.1.3 for details.
- 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.
    - 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 study discontinuation. The approach for partial and missing data is

described in Section 9.1.1 (Missing data approach will be identical to that of the primary endpoint).

- 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. See Section 9.1.4.1 for details.

- Mean change from Baseline in the Migraine-Specific Quality of Life Questionnaire Role Function, Restrictive domain (MSQ v2.1) at Week 12.
  - 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 study discontinuation.
  - 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. See Section 9.2.1.4 for details.

6. STUDY PATIENTS

6.1. Disposition of Patients

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.

6.2. Demographic and Other 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 meds, chronic migraine history, number of baseline headache days, number of baseline migraines, and baseline diary compliance (see section 7.3) will be summarized by treatment group (TNX-1900 and placebo) and overall for the mITT and Safety populations. Categorical items will be reported with counts and percentages; continuous items will be reported using summary statistics (mean, standard deviation (SD), median, minimum, maximum).

6.3. Prior and Concomitant Medications

Prior medications are defined as medications or therapies initiated prior to the start of the study drug and terminated prior to the start of study drug. Hence, these medications or therapies will have end dates prior to the first dose date of study drug. Concomitant medications are defined as any medications other than the study drug that a patient receives concurrently with the study drug. These medications will have end dates on or after the first dose date of the study drug if they have an end date. In the case of missing or partial dates, medications will be considered concomitant unless the available data excludes that possibility.

All medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior and concomitant medications will be summarized by treatment group and by the number and percentage of patients taking each medication, classified by using WHO-DD Anatomical Therapeutic Chemical Level 3 and preferred term.

Prior, but previously discontinued (prior to screening for the study), preventative migraine medications will be collected on a separate case report from (CRF) with additional information on the tolerability and efficacy of the medication. These will be summarized by treatment group and by the number and percentage of patients taking each medication (grouped by preferred term) as well as the number and percentage for each level of the patient reports of effectiveness and tolerability. Any preventative migraine medication used within 90 days of the Screening visit will be recorded on the Prior and Concomitant Medication CRF.

Additionally, prior other treatments or devices used within 90 days of the Screening Visit (ie. acupuncture, electrical or magnetic stimulating devices, chiropractor, PT, etc.) will be collected and tabulated by type of therapy.

All medications and therapies will be presented in listings, with prior preventative migraine medications listed separately.

6.4. Medical History

Medical History will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and Preferred Term using frequency counts and percentages by treatment group. Nasal Exam findings will be summarized using frequency counts and percentages by treatment group. Physical examination and nasal exam findings will be presented in listings.

7. STUDY OPERATIONS

7.1. Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or ICH Good Clinical Practice (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. Protocol deviations will be logged and categorized as important or non-important prior to unblinding. Protocol deviations will be summarized by type, status as important or non-important, and by treatment group for the Safety population.

Individual protocol deviations will be listed by patient.

7.2. Randomization

This is a double-blind study; unless otherwise specified, all study personnel are to remain blinded to study drug prior to database lock and final analysis following study unblinding.

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 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. Up to approximately 30% of the patients randomized into the study can be on 1 migraine preventative medication.

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.

7.3. Measures of Treatment Compliance

No direct measures of drug compliance will be captured via drug accountability. Compliance via the diary will be reported for the post-baseline period. Patients are asked to report whether they took their morning and evening doses; compliance will be reported as the number of "Yes" responses reported out of the total number of expected doses based on the dates the diary was issued and collected times 2 doses/day. The compliance will be summarized with descriptive statistics. Additionally, the number and percentage of patients with <70% compliance, 70% to <80%, 80% to <90%, and 90 to 100% compliance will be reported.

Additionally, compliance with diary completion will be reported and summarized with descriptive statistics. Dairy compliance will be defined as the number of days which have ANY data entered (even if partial/incomplete) divided by the number of days they were expected to complete the diary. This will be summarized for the baseline and post-baseline periods separately.

[redacted]

8. GENERAL ANALYSIS AND REPORTING CONSIDERATIONS

Descriptive summaries will be provided where appropriate for each of the primary and secondary variables. In general, tables will summarize data by treatment group and visit.

Continuous, quantitative variable summaries will include the number of patients (N) with non-missing values, mean, standard deviation, median, minimum, and maximum.

Categorical, qualitative variable summaries will include the frequency and percentage of patients who are in the particular category. In general, the denominator for the percentage calculation will be based upon the total number of patients in the study population for the treatment group unless otherwise specified.

Unless otherwise specified, baseline values are defined as the last non-missing measurement prior to the first dose of study drug. Change from baseline will be defined as the post-baseline visit value minus the baseline value.

For continuous endpoints where treatment groups are compared via linear models with the difference in LS means, the effect size will be calculated and included as a summary statistic using the difference in LS means and its standard error, transformed to a standard deviation. Study day is defined as assessment date – first dose date +1 for dates after the first dose date and assessment date – first dose date for dates prior to the first dose.

All analyses will be performed using SAS® Software version 9.4 or later.

8.1.1. Study Success

[redacted]

8.1.2. Multicenter Studies

This is a multicenter study. Unless otherwise specified, data from all study sites will be pooled for all analyses unless otherwise specified.

8.1.3. Assessment Time Windows

Patients who withdraw/drop out from the study will have the early termination (ET) data collected at their ET visit included in the analysis at the closest visit where a given assessment should be collected per the schedule of assessments (Week 4, 8, 12, 14), using midpoints

[redacted]

between visits to window the early termination. If this results in two records for a given visit, then the one closest to the targeted date will be used. Visits beyond day 112 (two weeks past the target day for Week 14) will not be mapped and reported with Week 14; they may appear in the last observation analyses described for safety endpoints.

Diary data will be grouped into 28 day "months" see section 9.1.1 for details.

8.1.4. Timing of Analyses

All final, planned analyses will be performed after the last participant has completed all study assessments, all relevant study data have been processed and integrated into the analysis database, and the database has been locked.

Any post-hoc, exploratory analyses completed to support planned study analysis, which were not identified in this SAP, will be documented and reported in appendices to the CSR. Any results from these unplanned analyses (post-hoc) will also be clearly identified in the text of the CSR.

8.1.5. Multiple Comparisons/Multiplicity

The overall type I error rate will be controlled at α=0.05 for the set of primary and key secondary endpoint comparisons between each dose level of active versus placebo using a graphical approach. Each of the dose comparisons to placebo will be assigned ½ the alpha for the primary endpoint of change in the number of migraine headache days from the last 28 days of Baseline to the last 28 days of treatment. The stronger of the p-values will be tested first at α=0.025 and if significant, 100% of its alpha will be passed to the other dose's primary comparison so that it is tested at α=0.05.

If this is significant, then this α=0.05 will be passed to the first secondary and split for the two dose comparisons to placebo on the endpoint of the proportion of patients experiencing a $\geq$ 50% reduction in the number of migraine headache days from Baseline to month 3. As above, the stronger of the p-values will be tested first at α=0.025 and if significant, 100% of its alpha will be passed to the other dose's secondary endpoint comparison (α=0.05). At each step, if a p-value fails to meet the alpha threshold for significance, the process will be halted and all subsequent comparisons declared non-significant. This will continue with the same pattern through the endpoints in the order listed below:

The order of the key secondary analyses will be:

- Proportion of patients experiencing a $\geq$ 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.

[redacted]

- 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 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 Role Function, Restrictive domain (MSQ v2.1) at Week 12.

The order of the other secondary analysis will be:

- 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.

The exploratory analyses will be:

- 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

Although all p-values will be non-significant following the first to fail to meet its alpha threshold, p-values will be reported for all the above endpoints; they will be noted as descriptive for those following the first non-significant p-value.

8.1.6. Power and 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. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9. ENDPOINT EVALUATION

9.1. Primary Endpoint

The primary efficacy endpoint will be the change in the number of 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, 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 (see Appendix 15.5)

9.1.1. Computation of the Primary Endpoint

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 for a month, the counts will be normalized to 28 days by taking 28* [migraine count] / [days of non-missing data]. The eDiary questions and derivation of migraine days are found in Appendix 15.4.

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.

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 mixed model repeated measures analysis will provide unbiased estimates under the assumption that data are missing at random (MAR).

9.1.2. Primary Analysis of the Primary Endpoint

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 an MMRM model with fixed effects of treatment, month, baseline value, treatment by month interaction, 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) with 95% CIs and p-values 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

[redacted]

estimate the standard errors of the fixed effects parameters and the denominator degrees of freedom will utilize the DDFM=BETWITHIN option in SAS®.

Additionally, Kruskal-Wallis tests will be performed and reported for each month, in case the migraine days do not adhere to model assumptions.

9.1.3. Sensitivity Analyses of the Primary Analysis

Three sensitivity analyses may be performed if the primary analysis is positive (statistically significant or strongly trending in favor of active treatment):

9.1.3.1. Missing at Random Multiple Imputation

Multiple imputation (MI) methodology will be utilized to impute complete datasets with three monthly observations for all patients in the mITT population. Monthly migraine counts will be computed as described in Section 9.1.1. This will yield 4 migraine count records per patient (baseline and 3 months follow-up). The missing values will be imputed for all patients/records using MI within each treatment group conditioned on each patients' non-missing data (including baseline), and the stratification factor. The Markov Chain Monte Carlo (MCMC) method will be used to produce 20 repeats of the data and seeds are given in appendix 15.2. LS means and differences across the twenty MI reps will be combined using SAS procedure MIANALYZE (Rubin, 1976).

9.1.3.2. Multiple Imputation Tipping Point

A tipping point analysis will be performed using the above MI datasets and applying an increasing delta (of higher migraine counts) to the active groups until statistical significance is no longer achieved. The delta will only be applied to imputed values; this will be done in 0.5 migraine day increments. This will only be performed if the primary analysis is significant. This will test the overall robustness of the primary analysis.

9.1.3.3. Missing Not at Random Multiple Imputation

Finally, a missing-not-at-random multiple imputation approach will be utilized taking into account the reason for discontinuation.

Missing monthly migraine counts for participants in the mITT population will be imputed via multiple imputation (MI). [redacted]

[redacted]

[redacted]

9.1.4. Secondary Analyses of the Primary Endpoint

Two additional analyses of the number of headache days will be performed:

9.1.4.1. Mean Change Over the Full 12 Week follow-up

The 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 will be compared among the treatment groups. This will utilize the same model and output as the primary analysis, but will report model contrasts averaging the three follow-up months. Least square means (LSMs), standard errors, and the LSM differences (each treatment vs placebo) will be reported for these averages.

9.1.4.2. Patients Experiencing a ≥ 50% Reduction in Migraine Headaches

Finally, for each patient and month, patients will be flagged as responders if they experience a ≥ 50% reduction in the number of migraine headache days from the last 28 days of Baseline to the given month's 28-day normalized migraine headache days. The percent change from baseline will be calculated for each month as 100*[monthly count– baseline count] / [baseline count]. The number and percentage of patients achieving ≥50% improvement will be reported as well as 95% CIs for the percentages. Patients with missing data will be considered non-responders/ not achieving either improvement threshold. The difference in percentages in the active and placebo arms from the Cochran-Mantel-Haenszel (CMH) common risk difference estimator will 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 CMH stratified by preventive medication use. The primary time point of interest will be month 3, but each month will be summarized.

[redacted]

9.2. Secondary Endpoints

All secondary efficacy analyses will be based on the mITT population.

9.2.1. Key Secondary Endpoints

There will be six key secondary 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 (described in Section 9.1.4.2 above).
- 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 (described in Section 9.1.4.1 above).
- Mean change from Baseline in the Migraine-Specific Quality of Life Questionnaire Role Function, Restrictive domain (MSQ v2.1) at Week 12.

9.2.1.1. Rescue Medication Use

The Mean change in the number of days using rescue medication from the last 28 days of Baseline to the last 28 days of treatment will be compared among the treatment groups. A rescue medication use day is any calendar day (0:00 to 23:59) in which the patient records the use of a triptan, ergot derivative, or other migraine-specific abortive medication (see Appendix 15.5). Calculation and analysis of this will be identical to the primary with the substitution of days using rescue medication for migraine days. Least square means (LSMs), standard errors, and the LSM differences (each treatment vs placebo) will be reported for these averages. As with the primary endpoint, Kruskal-Wallis tests will be performed and reported.

9.2.1.2. Patient Global Impression of Change

The number and percentage and 95% CIs for the percentages will be reported for patients with a PGIC rating of 1, "very much improved", or 2, "much improved", at Week 12 for each treatment group. Patients with missing data will be considered non-responders. The difference in percentages in the active and placebo arms will reported along with its 95% CI (using the Sato estimator of variance). Pairwise p-values will compare each treatment arm to placebo based on a

[redacted]

CMH stratified by preventive medication use. The primary time point of interest will be Week 12, but each time point collected will be summarized.

9.2.1.3. Mean Change in Moderate or Severe Headaches

The 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 (i.e. month 3) will be compared among the treatment groups. A moderate or severe headache day is any calendar day (0:00 to 23:59) in which the patient records an attack of moderate or severe peak intensity in the e-diary. Calculation and analysis of this will be identical to the primary with the exception that only days with moderate or severe headache will be included in the tally. Least square means (LSMs), standard errors, and the LSM differences (each treatment vs placebo) will be reported for these averages. As with the primary endpoint, Kruskal-Wallis tests will be performed and reported.

9.2.1.4. Mean Change in in the Migraine-Specific Quality of Life Questionnaire (MSQ)

For the MSQ v2.1, items are scored 1-6; the total and three sub-domains will be calculated and scaled such that the resulting values will be scaled 0-100, with higher scores indicating better quality of life. The Role Function, Restrictive domain will be a key secondary endpoint and the other items & total will be additional secondary endpoints.

The total MSQ will be calculated as the sum of the 14 individual questions, minus 14, then scaled by 100/70. Missing values will be imputed with the means of the non-missing values, as long as there are at least 7 non-missing values.

Role Function – Restrictive: Items 1-7 will be summed, then 7 subtracted from the value, and this scaled by 100/35. Missing values will be imputed with the means of the non-missing values, as long as there are at least 4 non-missing values. If there are less than 4 values, then the score will be set to missing.

Role Function – Preventative: Items 8-11 will be summed, then 4 subtracted from the value, and this scaled by 100/20. Missing values will be imputed with the means of the non-missing values, as long as there are at least 2 non-missing values. If there are less than 2 values, then the score will be set to missing.

Emotional Function: Items 12-14 will be summed, then 3 subtracted from the value, and this scaled by 100/15. Missing values will be imputed with the means of the non-missing values, as long as there is at least 1 non-missing value. If there are less than 2 values, then the score will be set to missing.

Summary statistics (mean, SD, median, minimum, maximum) will be reported for the change from the baseline in each MSQ v2.1 score to each visit and for each of the treatment groups. The change from baseline will be analyzed in an MMRM model with fixed effects of treatment, visit, baseline value, treatment by visit interaction, and stratification factor (preventive medication use); an unstructured covariance matrix will be used. LSMs, standard errors, and the LSM differences (each treatment vs placebo) with 95% CIs and p-values will be reported for each visit (with week 12 being of primary interest). 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®.

9.2.2. Additional Secondary Endpoints

Each of the following continuous endpoints will be summarized:

- Mean change from Baseline in the Hospital Anxiety and Depression Scale (HADS) at Week 12.
- Mean change from Baseline in the Migraine Disability Assessment questionnaire (MIDAS) Test 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.

For each, summary statistics (mean, SD, median, minimum, maximum) will be reported for the change from the baseline to each visit and for each of the treatment groups.

For HADS the change from baseline will be analyzed in an MMRM model with fixed effects of treatment, visit, baseline value, treatment by visit interaction, and stratification factor (preventive medication use); an unstructured covariance matrix will be used. LSMs, standard errors, and the LSM differences (each treatment vs placebo) with 95% CIs and p-values will be reported for each visit (with week 12 being of primary interest). 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®.

MIDAS and CSFQ are only collected at baseline and week 12, thus they will be modeled in a ANCOVA similar to the MMRM used for the repeated measures. The model will include fixed effects for treatment, baseline, and stratification factor (preventive medication use). LSMs, standard errors, and the LSM differences (each treatment vs placebo) with 95% CIs and p-values will be reported.

9.2.3. 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.

[redacted]

A headache day is any calendar day (0:00 to 23:59) in which the patient records an attack (a headache or a migraine) in the e-diary.

For the first two exploratory endpoints, the difference in percentages in the active and placebo arms will reported along with its 95% CI (using the Sato estimator of variance). Pairwise p-values will compare each treatment arm to placebo based on a CMH stratified by preventive medication use. Patients with missing data will be considered non-responders.

Calculation and analysis of the number of headache free days will be identical to the primary with the exception that outcome of interest will be days without headaches. Least square means (LSMs), standard errors, and the LSM differences (each treatment vs placebo) will be reported for these averages. As with the primary endpoint, Kruskal-Wallis tests will be performed and reported.

[redacted]

10. SAFETY EVALUATION

10.1. Overview of Safety Analysis Methods

All safety analyses will be completed for the Safety Population. All safety data will be tabulated and listed. No formal statistics or imputation will be performed for the safety analysis. The analysis of safety assessments in this study will include summaries of the following safety and tolerability data collected for each patient:

- Extent of exposure
- Incidence of Adverse Events
- Changes from baseline in clinical laboratory results
- Changes from baseline in vital signs
- Changes from baseline in electrocardiograms
- Monitoring suicidality using the Columbia Suicide Severity Rating Scale (C-SSRS)
- Changes from baseline in the HADS scores
- Changes from baseline in the CSFQ-14

10.2. Extent of Exposure

Duration of exposure will be calculated and summarized with descriptive statistics. The duration of exposure will be the date of last dose – date of the first dose +1, based on the first and last doses as recorded on the CRF.

Exposure days (number of days on study drug) is defined as the total number days reported in the diary that the patient took study drug. If the first dose date or last dose date from the CRF is not among the diary-reported dates, that day is added to the tally.

The duration of exposure and exposure days will be tabulated with summary statistics by treatment group. Additionally, the number of patients with duration of exposure by weeks (≤4 weeks, 4 to ≤8, 8 to ≤12, and >12 weeks) will be presented.

10.3. Adverse Events

An adverse event (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.

[redacted]

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. In the case of missing or partial dates, an adverse event will be considered treatment-emergent unless the available data excludes that possibility.

An AE summary table will present totals for the following:

- All treatment-emergent adverse events (TEAEs)
- TEAEs by severity
- TEAEs leading to study drug discontinuation
- TEAEs by relationship (not related, unlikely related, possibly related)
- SAEs
- AEs of Special Interest (AESIs [See below])

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

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

All AEs will be presented in a listing.

These summaries will include SAEs; additionally, they will be presented separately (see below).

10.4. Deaths, Serious Adverse Events, and Other Significant Adverse Events

Summaries of incidence rates (frequencies and percentages) of individual SAEs by MedDRA SOC and preferred term will be presented. Additionally, SAEs will be listed separately.

Since intranasal 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 (AESI); nasal cavity AEs will be identified on the CRF and additional information collected regarding the frequency, duration and temporal relationship to dosing. This information will be tabulated for the nasal cavity AEs and presented in a listing.

AESIs and TEAEs leading to discontinuation of study drug will be analyzed and presented in a manner identical to the SAEs.

Adverse events potentially related to abuse will be presented in a separate listing; terms to be used are given in Appendix 15.3. These will be compared against the current coding dictionary and any related or similar terms will be included; additional terms may be added if they are thought to potentially be related to abuse.

All deaths will be reported in a listing.

[redacted]

10.5. Clinical Laboratory Evaluation

Laboratory data including Chemistry, Hematology, and urinalyses will be summarized by treatment and visit for the Safety Population. Descriptive summaries of actual values and changes from baseline will be presented by study visit and last assessment for each clinical laboratory analyte and for each treatment group. 95% confidence intervals will be presented for change from baseline.

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

Results of urine drug screens and pregnancy tests will be presented in listings.

10.6. Vital Signs, Electrocardiograms, Physical Findings, and Other Observations Related to Safety

10.6.1. Vital Signs

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from baseline at each assessment time point and last assessment will be calculated for vital signs including weight, body mass index, body temperature, pulse rate, systolic blood pressure and diastolic blood pressure. 95% confidence intervals will be presented for change from baseline. Vital sign values, including abnormal values, will be listed.

10.6.2. Electrocardiograms (ECGs)

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from baseline at each assessment time point and last assessment will be calculated for each electrocardiogram parameter. 95% confidence intervals will be presented for change from baseline. Additionally, the number and percentage of patients with normal, abnormal/not clinically significant, and abnormal/ clinically significant ECG interpretations will be summarized at each assessment time point and last assessment. Percentages will be out of the number of subjects in the safety population. Electrocardiogram values, including clinical interpretation values, will be listed.

10.6.3. Physical Examinations

Physical examination data will be presented in a data listing.

10.6.4. Other Safety Measures

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

Based on the C-SSRS results, the overall number of patients with lifetime and/or current suicidal ideation (by item and category), suicidal behavior (by item and category), or self-injurious

[redacted]

behavior at the screening and baseline visit will be summarized by visit and treatment group. Additionally, the overall number of patients with any suicidal ideation or behavior (by type and in total) or self-injurious behavior while on-treatment will be provided by treatment group. Patients will only be counted once for on-treatment ideation and on-treatment behavior, at the worst-case response for each item.

10.6.4.2. Changes from baseline in the HADS scores

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from baseline at each assessment time point and last assessment will be calculated for both HADS domain scores. Note that the HADS is considered both an efficacy and safety endpoint.

10.6.4.3. Changes from baseline in the Sexual Functioning Questionnaire Short-Form (CSFQ-14)

The CSFQ-14 will be analyzed by gender. Note: there is a male version and female version for the CSFQ-14. Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from baseline at each assessment time point and last assessment will be calculated for each CSFQ domain score and the total. Note that the CSFQ is considered both an efficacy and safety endpoint.

[redacted]

11. OTHER ANALYSES

N/A

[redacted]

12. INTERIM ANALYSES

An interim analysis will not be performed in this study.

[redacted]

13. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

14. REFERENCES

Diggle P, Kenward M. Informative dropout in longitudinal data analysis (with discussion). Appl Stat. 1994;43:49-93

Rubin, D. B. (1976), “Inference and Missing Data,”Biometrika, 63, 581–592.

[redacted]

15. APPENDIX

15.1. Schedule of Events

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	**1 Day –63 to -28 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]

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	**1 Day –63 to -28 days** **Day -49 to Day -1**	**Day 1**	**Day 29 ± 4d**	**Day 57 ± 4d**	**Day 85 ± 4d**	**Day 99 ± 4d**
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					
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	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		

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	**1 Day –63 to -28 days** **Day -49 to Day -1**	**Day 1**	**Day 29 ± 4d**	**Day 57 ± 4d**	**Day 85 ± 4d**	**Day 99 ± 4d**
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	

[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.

15.2. Random Seeds

The following list of numbers will be used for random seeds where required for MI processes:

3954748

5375852

1235264

2575945

9454116

2624285

1783458

6572845

9458932

7855785

These will generally be used in order for the primary analysis, then secondary endpoints and sensitivity analyses. For cases where identical code may be applied to more than one outcome or a sensitivity analysis that uses a minor variation on the primary code, the second to last digit will be incremented by 1 to produce new seeds for the subsequent outcome/analysis. If a single dataset requires more than the 10 seeds above, additional seeds will be generated by incrementing the last digit by 1. All seeds used will be documented in the programming specifications and the programs themselves.

15.3. AEs Potentially Related to Abuse

The following preferred terms will be used to identify AEs potentially related to abuse.

- Euphoric mood
- Elevated mood
- Feeling abnormal
- Feeling drunk
- Feeling of relaxation
- Dizziness
- Thinking abnormal
- Hallucination
- Inappropriate affect
- Psychosis
- Aggression
- Confusion
- Disorientation
- Drug tolerance

[redacted]

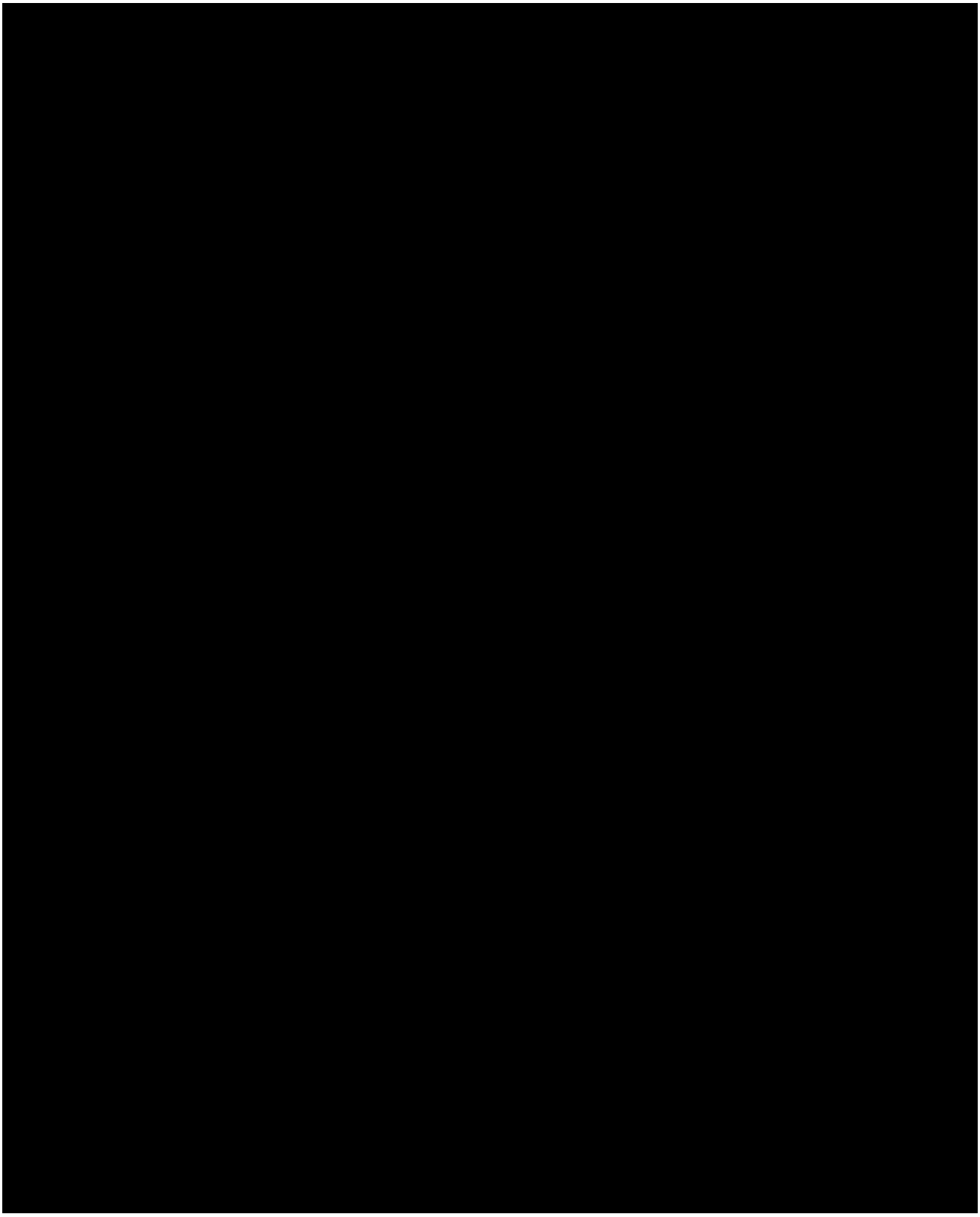
- Habituation
- Drug withdrawal syndrome

[redacted]

15.4. Electronic Diary Questions and Derivation of Migraines/Headaches

QUESTION	RESPONSES
Q1. Did you have a headache yesterday?	Yes
	No
Q2. Did you experience a migraine with aura yesterday?	Yes
	No
Q3. How long did your headache last?	a. 4 hours or more b. at least 2 hours but less than 4 c. less than 2 hours
Q4. How severe was your headache pain yesterday at its peak?	Mild
	Moderate
	Severe
The following questions refer to yesterday:	
Q5. Was the headache throbbing, pulsating, or pounding?	Yes
	No
Q6. Was the headache pain on only one side of your head?	Yes
	No
Q7. Was the headache made worse by your usual daily activities such as walking or climbing stairs?	Yes
	No
Q8. Did light bother you (did you have photophobia)?	Yes No
Q9. Did sound and noise bother you (did you have phonophobia)?	Yes
	No
Q10. Did you have nausea or vomiting?	Yes
	No
Q11. Did you take any headache medications yesterday?	Yes
	No
Q12. Please add medications taken. (*drop down list name, route, dosage, and number of doses will be collected*)	
Q13. Did you take any pain medications yesterday besides a medication for a headache or migraine?	Yes No
Q14. Please add medications taken for any issue other than a headache. (*drop down list name, route, dosage, and number of doses will be collected*)	
Q15. Was your headache yesterday a migraine and was it relieved by the medication you took?	Yes
	No

For treatment phase only, log morning and evening doses.



[redacted]

[redacted]

[redacted]

15.5. Rescue Medications

The following is a partial list of medications that will be considered migraine-specific abortive medications. In general, triptans and ergot derivatives will be included; all medications will be reviewed and a final list will be documented prior to unblinding.

[redacted]

[redacted]

[redacted]

[redacted]

16. ATTACHMENTS

N/A

[redacted]