Statistical Analysis Plan

Protocol Title:	A 12-Week Open-Label Extension Study to Evaluate TNX-102 SL Taken Daily at Bedtime in Patients with PTSD
Protocol Number:	Protocol No. TNX-CY-P303 (17MAR2017); Amendment 1, Dated 31MAR2017
Investigational Product:	Tonmya®/TNX-102 SL (cyclobenzaprine HCl sublingual tablets), 2.8 mg
Dose	5.6 mg taken daily at bedtime as two 2.8 mg sublingual tablets
Phase:	3
Sponsor:	Tonix Pharmaceuticals, Inc. [redacted]
SAP Author:	[redacted]
SAP Version:	Final 1.0
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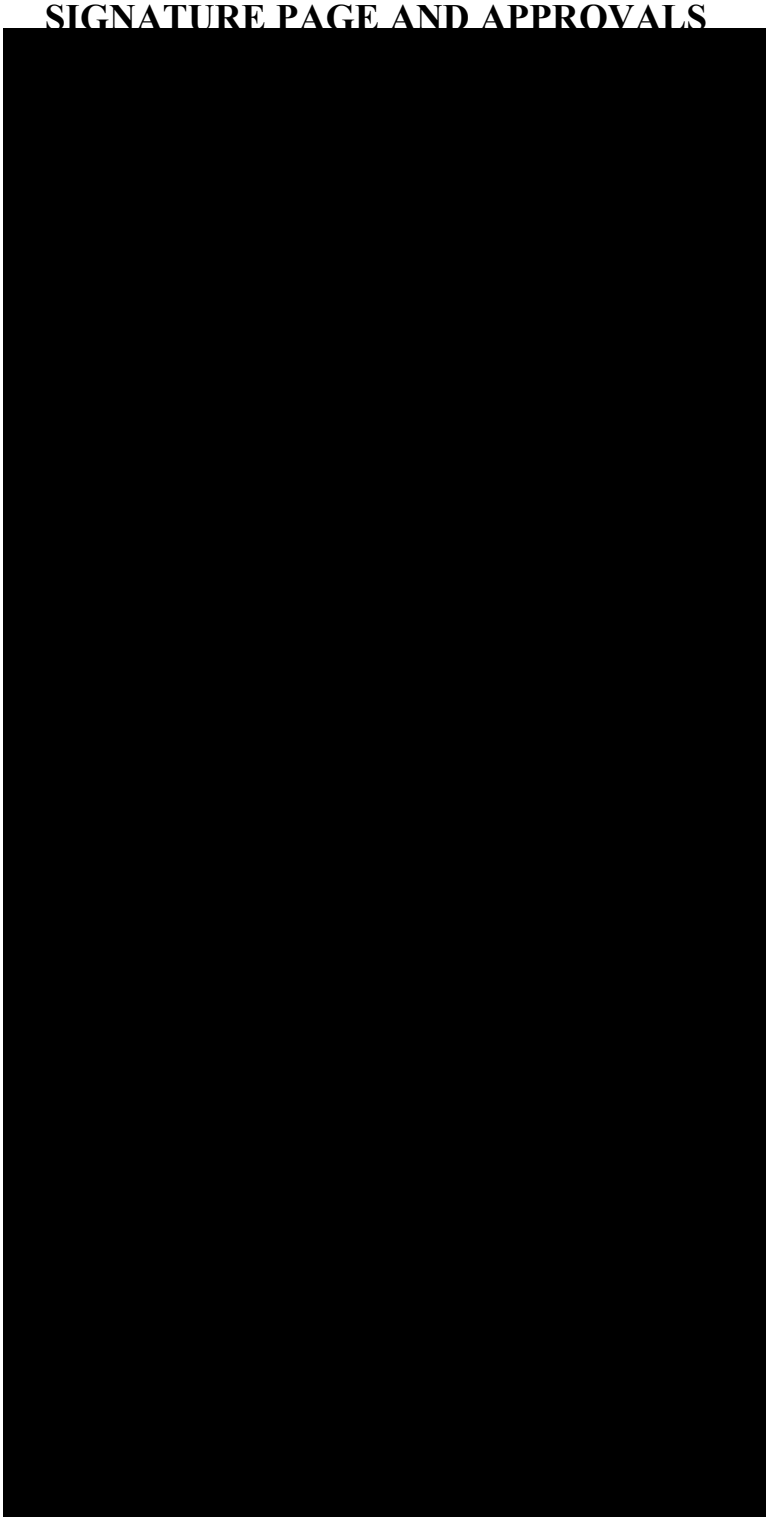

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ABBREVIATIONS

ABBREVIATION	DEFINITION OR DESCRIPTION
AE	Adverse Event
ADaM	Analysis Data Model
ANCOVA	Analysis of Covariance
BDI-II	Beck Depression Inventory–II
BMI	Body Mass Index
CA-AF	Criterion A – Assessment Form
CAPS-5	Clinician Administered PTSD Scale (for DSM-5)
CGI-I	Clinical Global Impression- Improvement from Initiation of Treatment
CI	Confidence Interval
CMH	Cochran Mantel Haenszel
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (Version 4)
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (Version 5)
ECG	Electrocardiogram
EDC	Electronic Data Capture
e.g.	*Exempli gratia* (for example)
EMA	European Medicines Agency
ET	Early Termination
FDA	Food and Drug Administration
HCl	Hydrochloride
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
i.e.	*id est* (that is)
IWRS	Interactive Web Response System
LS	Least Squares
MAR	Missing at Random
MDE	Major Depressive Episode
MedDRA	Medical Dictionary for Regulatory Activities
Military-Related	Related to service in any branch of the armed services (active or veteran), or as a military contractor
MINI	Mini International Neuropsychiatric Interview
MMRM	Mixed Model Repeated Measures
N, n	Number (of participants)
NEAE	Newly Emergent Adverse Event
NIH	National Institutes of Health
PGIC	Patient Global Impression of Change Scale
PROMIS	Patient-Reported Outcome Measurement Information System
PTSD	Posttraumatic Stress Disorder
REML	Restricted Maximum Likelihood

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SD	Standard deviation
SDS	Sheehan Disability Scale
SDTM	Study Data Tabulation Model
SE	Standard Error
SL	Sublingual
SOC	System Organ Class
TNX-102 SL	Cyclobenzaprine HCl sublingual tablets
WHO-DD	World Health Organization Drug Dictionary

1. OVERVIEW

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for protocol TNX-CY-P303: A 12-Week Open-Label Extension Study to Evaluate TNX-102 SL Taken Daily at Bedtime in Patients with PTSD (17MAR2017); Amendment 1, Dated 31MAR2017.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by FDA, European Medicines Agency (EMA), and International Council for Harmonization (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, published by the American Statistical Association and the Royal Statistical Society, for statistical practice.

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.

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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 related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective of the study is to evaluate the safety of TNX-102 SL taken daily at bedtime over an additional 12 weeks in patients with PTSD who have completed a double-blind lead-in study.

2.1.2 Secondary Objectives

The secondary objective is to evaluate the safety of TNX-102 SL 5.6 mg taken at bedtime over 12 weeks of treatment.

2.2 Study Endpoints

2.2.1 Efficacy Endpoints

Comparisons will be made at each study week of data collection to both the baseline of this study (P303) and the baseline from the double-blind study (P301) and described in section 7.1.

Efficacy endpoints include:

- Change from both baselines in the total CAPS-5 score
- Proportion of patients with a CGI-I score of "very much improved" or "much improved"
- from both baselines
- Change from both baselines in the SDS total score
- Change from both baselines in the individual items assessed using the SDS
- Change from both baselines in patients' quality of sleep using the PROMIS Sleep Disturbance scale
- Change from both baselines in CAPS-5 symptom cluster subscores
- Proportion of patients with a ≥50% improvement from baseline (both baselines) in total
- CAPS-5 score
- Change from both baselines in BDI-II score

2.2.2 Safety Endpoints

Safety will be assessed by:

- Adverse events (AE) and serious AEs (SAEs) throughout the entire duration of the study, including detailed assessment of AEs involving the oral cavity.
- Changes from both baselines in clinical laboratory test results.
- Changes from both baselines in vital signs and weight.
- Change from both baselines in BDI-II.
- Suicidal ideation or behavior as reported on the Columbia Suicide Severity Rating Scale (C-SSRS).

3. OVERALL STUDY DESIGN AND PLAN

This is a 12-week, multicenter, open-label extension study designed to accumulate additional safety exposure and efficacy data with daily bedtime dosing of TNX-102 SL 5.6 mg (2 x 2.8mg tablets) in patients with PTSD. This study will be conducted at approximately 35 sites in the United States (US).

Patients who have completed participation in a Phase 3, randomized, double-blind, placebo controlled study comparing TNX-102 SL 5.6 mg versus placebo for the treatment of PTSD will be eligible. This extension study consists of 5 visits, including the Screening/Baseline visit (which is anticipated to be the same as the primary outcome visit in the double-blind lead-in study), a telephonic visit at week 2, and in-clinic visits after 4, 8 and 12 weeks of treatment (Visits 3-5). The total treatment duration of this study will be 12 weeks. Therefore, the maximum total duration of continuous treatment with TNX-102 SL could be approximately 24 weeks for those patients assigned to active study drug in the lead-in study.

Patient data collected at the Week 12 visit in the lead-in study will be used as one of the defined baselines for this study. There is no need to repeat assessments at Visit 1 for this study, if they were collected in the lead-in study and patients enroll and initiate study treatment within fourteen days of completing the lead-in study. After the patient has completed his/her participation in the lead-in study and has consented to participate in this open-label extension study, patients will be dispensed a 4-week supply of open-label TNX-102 SL tablets and will be instructed to take the study drug sublingually daily at bedtime, starting on the evening of Visit 1. A phone visit will be completed after 2 weeks of treatment and patients will return to the study center for safety and efficacy assessments at Weeks 4, 8, and 12 (or early termination). At the Weeks 4 and 8 visits patients will return their TNX-102 SL medication and will receive another 4-week supply. Patients will be allowed to take medications deemed appropriate by their health care providers to manage their PTSD and other conditions, including currently approved PTSD therapies.

3.1 Selection of Study Population

For a complete list of inclusion and exclusion criteria please refer to the initial protocol issued March 17, 2017 and Amendment 1, dated March 31, 2017.

3.2 Method of Treatment Assignment and Randomization

All patients will be assigned to TNX-102 SL, 5.6 mg regardless of which treatment arm they were randomized to in the lead-in study. No patients or site personnel will know what the prior treatment was in the double-blind lead-in study.

Throughout this document, when describing analyses performed by treatment group, this will refer to the treatment that the subject was randomized to in the double-blind lead-in study.

4. ANALYSIS AND REPORTING

4.1 Final Analysis

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.

5. SAMPLE SIZE DETERMINATION

No sample size calculations were made for this study as it is a follow-on, open-label study. The sample size for this study will depend upon the number of patients who complete the lead-in study, remain eligible for entry, and indicate willingness to participate in this extension study.

6. ANALYSIS POPULATIONS

The following analysis populations are planned for this study:

- **Safety Population (SAFETY):** All participants who receive at least 1 dose of study drug. Participants who are issued study drug, but return 100% of it (i.e., none consumed) will be excluded from the safety population; likewise, participants that have no follow up following receipt of study drug to indicate they took drug are excluded. All safety analyses and demographic/baseline characterization will be performed using this population.

7. GENERAL ISSUES FOR STATISTICAL ANALYSIS

7.1 General Statistical Methodology

Descriptive summaries will be provided where appropriate for each of the primary and secondary variables. In general, tables will summarize data by treatment group that the subjects were randomized to in the prior study and visit.

All tables will be completed for the Safety Population unless otherwise specified

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

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

Two baselines will be utilized for most analyses: P301 baseline values are defined as the last non-missing measurement prior to the first dose of double-blind study drug in study P301; likewise, P303 baseline values are defined as the last non-missing measurement prior to the first dose of open-label study drug in study P303. Change from baseline will be defined as the post-baseline visit value minus the baseline value and will be calculated for both baselines.

ET participants will only be followed if required to monitor an on-going adverse event or other condition.

Participants are not supposed to change study sites; however, should this be necessary to allow a participant to continue in the study, participants will be analyzed under the site where they were initially enrolled.

Study day after first dose is defined as assessment date – first dose date +1. Dates prior to first dose are defined as assessment date – first dose date. Note that the protocol refers to "Day 0"; for the purposes of the datasets and analyses, this would appear as day 1.

All analyses will be performed using Statistical Analysis System (SAS®) Software version 9.4 or later.

Unless otherwise noted, 95% confidence intervals will be presented for statistical tests.

7.1.1 Adjustments for Multiplicity and Other Alpha Control

7.1.1.1 Multiplicity

No adjustments will be made from multiplicity and all p-values will be nominal.

7.1.2 Data Handling for Participants Who Discontinue Study Drug or Withdraw from the Study

Participants who withdraw/drop out from the study will have their ET visit data collected and included in the analysis based on the closest visit window (Week 4, 8 or 12). Visit windows will be assigned by splitting the periods between visits at the midpoint between

the visits. If more than one record falls within the window, the one closest to the target date will be used in the analysis, with preference given to the scheduled visits in the case of equidistant visits.

7.2 Efficacy Assessments

There is no formal testing order to the efficacy assessments in this protocol; however, they are described below in approximate order of importance.

7.2.1 Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)

The primary efficacy endpoint is the change from baseline in total CAPS-5 score at Week 12 (Visit 6).

The CAPS-5 is an updated and validated version of a semi-structured interview that has been designed to assess the essential features of PTSD as defined by the DSM-5 (Weathers et al, 2013). The CAPS-5 affords the clinician flexibility to inquire about symptoms and diagnostic status over different time frames, such as past week, past month, and/or worst month for lifetime. For this study, a "Diagnostic" version of the CAPS-5 (past month recall) will be utilized at the Screening visit to confirm the diagnosis of PTSD and determine eligibility. A "Symptom Severity" version of the CAPS-5 (past week recall) will be completed by the clinician at all other time points (Baseline [Visit 2] and after 12 weeks of treatment [Visits 6]).

The CAPS-5 interview contains the following components

- Life Events Checklist for DSM-5 (LEC-5): Completed by the participant at the Screening Visit (Visit 1 only)
- Criterion A – Assessment Form (CA-AF): this semi-structured interview is based on the Criterion A discussion included in the CAPS-5, but modified (by Dr. Frank Weathers, CAPS-5 lead author) specifically for this study to ensure sufficient review of the traumas outlined on the participant-completed LEC-5 and to capture clear description of the participant's index/qualifying trauma (Visit 1 only)
- PTSD symptoms, onset/duration, distress/impairment, global rating, and dissociative symptoms:
    - o Criterion B: Items 1-5 (Intrusion symptoms)
    - o Criterion C: Items 6-7 (Avoidance symptoms)
    - o Criterion D: Items 8-14 (Negative alterations in cognitions & mood)
    - o Criterion E: Items 15-20 (Arousal and reactivity symptoms)
    - o Criterion F: Items 21-22 (Onset and duration of symptoms)
    - o Criterion G: Items 23-25 (Distress and impairment due to PTSD)
    - o Global ratings: Items 26-27 (Validity, severity)
    - o Dissociative symptoms: Items 29 (Depersonalization) and 30 (Derealization)

In addition to the total symptom score (obtained from the sum of Criteria B-E), the CAPS-5 affords the opportunity to examine clusters of symptoms, including Criterion B

(intrusion symptoms), Criterion C (persistent avoidance), Criterion D (negative cognitions and mood), and Criterion E (arousal and reactivity), all of which will be secondary efficacy endpoints.

In the case of CAPS-5 items that are not resolvable at the site level (via query, review of source), the following conventions will be employed for handling of missing CAPS-5 items:

- For ≤ 2 missing item scores in Criterion B, D, or E, the average of the other items within the criterion will be used for the missing item;
- For < 2 missing items scores in Criterion C, which only has 2 items, the value of the non-missing items will be used for the missing item;
- For > 2 missing items in Criterion B, D, or E, or > 1 missing item in the Criterion C, the total CAPS-5 score will be considered missing overall.

7.2.2 Clinician Global Impression of Improvement (CGI-I)

The CGI-I will be completed by an Investigator to evaluate the participant's status since initiation of treatment. The CGI-I, status since initiation of treatment, is the first key secondary efficacy endpoint in this study. The CGI-I should be completed toward the end of each in-clinic post-Baseline study visit once all other assessments are available for the investigator's review. Once the participant has been randomized, an Investigator completes the CGI-I assessment after 4, 8, and 12 weeks of treatment in order to assess the overall change in the participant's status and answer the following question:

Since the initiation of treatment at Visit 2, the participant is:

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

The key secondary analysis of CGI will treat it as a continuous variable (scored 1-7 as above). There will be an additional outcome presented where a responder on the CGI-I is defined a participant who is scored as 'Very much improved' or 'Much improved' and compared between the study arms.

7.2.3 Sheehan Disability Scale (SDS)

The SDS scale is a self-report questionnaire that was designed to assess the participant's view of the degree to which symptoms have disrupted work/school, social life/leisure activities, and family life/home responsibilities during the previous two weeks (Sheehan & Sheehan, 2008). In addition, the SDS asks the participant to provide the number of days of work/school lost as well as unproductive days in the past two weeks. The SDS scale will be completed by the participant at Baseline and after 12 weeks of treatment (Visits 6). A total score will be calculated summing the three individual 11-point (0-10)

scales. For participants that do not respond to the work/school disruption because the participant checked the box indicating he/she has not worked or attended school for reasons unrelated to the disorder (PTSD), the total score will sum the other two domain questions and multiply by 1.5 (rounding up to the nearest whole number) to maintain the scale of 0-30 for the total score. Participants with missing values on the other items will be missing for the total.

7.2.4 Other Efficacy Outcomes

7.2.4.1 PROMIS Sleep Disturbance Instrument

PROMIS refers to the Patient-Reported Outcome Measurement Information System (www.nihpromis.org), a National Institutes of Health (NIH)-funded initiative to develop instruments to be used across chronic conditions.

The PROMIS sleep disturbance scale (short form 8a) will be assessed at Baseline and after 12 weeks of treatment (Visits 6).

The sleep disturbance scale will be calculated summing the individual item scores of the 8 items. These summed scores will be transformed to T-scores using the published conversions (see Section 14.2).

7.2.4.2 BDI-II

The Beck Depression Inventory (BDI-II) is a 21-item measure of the severity of current depressive symptoms, extensively validated for use in both medical and mental health populations. While this instrument does not provide a psychiatric diagnosis of depression and has considerable overlap with PTSD associated symptoms, it does provide a continuous scale for measuring changes in the severity of symptomatology. The BDI-II will be completed by the participant at all visits.

7.3 Safety Assessments

Safety will be assessed by:

- AE and SAEs throughout the entire duration of the study, including detailed assessment of AEs involving the oral cavity.
- Changes from both baselines in clinical laboratory test results.
- Changes from both baselines in vital signs and weight.
- Change from both baselines in BDI-II (see Section 7.2.4).
- Suicidal ideation or behavior as assessed by the C-SSRS.

7.3.1 Adverse Event and Prior/Concomitant Medication handling conventions

To handle missing or partial AE and prior/concomitant medication dates, the following rules will be applied.

For partial start dates:

1. If the year is unknown, then do not impute the date but assign a missing value.
2. If the month is unknown, then:
    a. If the year matches the year of the first dose date, then impute the month and day of the first dose date.
    b. Otherwise, assign "January."
3. If the day is unknown, then:
    a. If the month and year match the month and year of the first dose date, then impute the day of the first dose date.
    b. Otherwise, assign "01."

For partial end dates:

1. If the year is unknown, then do not impute the date but assign a missing value.
2. If the month is unknown, then assign "December."
3. If the day is unknown, then assign the last day of the month.

After implementing the rules above, to determine whether medications with missing start or stop dates are prior or concomitant medications, the following strategy will be used:

1. If the start date and stop date are both missing, then the most conservative approach is taken and the medication is considered to be a concomitant medication.
2. If the start date is missing but the stop date is not missing and is after the day of first study dose administration, then the most conservative approach is taken and the medication is considered to be concomitant.
3. If the start date is missing but the stop date is not missing and is on or before the day of first study dose and after the date of signed informed consent, then the medication is considered to be a prior medication.
4. If the start date is not missing but the stop date is missing, then the most conservative approach is taken and medication is considered to be concomitant.

The missing severity of an AE will be imputed to "severe"; the missing relationship to study drug of an AE will be imputed to "related".

8. STUDY PARTICIPANTS AND DEMOGRAPHICS

8.1 Disposition of Participants and Withdrawals

The numbers and percentage of participants entering, completing the study, and withdrawing from the study, along with reasons for withdrawal, will be tabulated overall and by treatment group. This summary will be based on all participants who have data entered into the database.

8.2 Protocol Deviations

Protocol deviations will be checked on complete data for all participants, determined during a data review meeting before database lock and the final analysis.

Protocol deviations will be summarized by type and by treatment group for the Safety population. Protocol "violations" are not differentiated from deviations; instead, each deviation is identified either as "major" or "minor" depending upon its potential impact upon the integrity of the study data or the participant's well-being.

Individual participants with protocol deviations will be listed.

8.3 Demographics and Other Baseline Characteristics

Descriptive summaries of the demographic and other baseline characteristics will be completed for all participants in the safety population by treatment groups, unless otherwise specified.

Descriptive summaries of demographic and other baseline conditions will include:

- Demographics (age, gender, race/ethnicity, height, weight, body mass index (BMI), family status, education, presence of current MDE, current nicotine, alcohol and THC usage, and employment status). In addition to the safety population, these will also be repeated for all randomized participants and the mITT population.
- CAPS-5 Assessment (Diagnostic version)

Other assessment's baseline values will be reported with their respective follow-up measures.

Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 and summarized by System Organ Class (SOC) and Preferred Term using frequency counts by treatment group. Note that the medical history is collected in the lead-in study; this analysis displays that information for the population of subjects that entered this study.

9. EFFICACY ANALYSES

9.1 Continuous Outcomes

The mean change from each baseline in the continuous outcome of interest will be analyzed using a restricted maximum likelihood (REML) based repeated measures approach, without imputation. The model will include all participants in the safety population. The dependent variable will be the observed change from baseline each in outcome at each post-randomization visit.

9.1.1 Efficacy Analysis Model

Continuous endpoints collected at baseline and Week 12 will be analyzed in an analysis of covariance model (ANCOVA) for the change from each baseline (P301 baseline and P303 baseline) in separate, independent models. The model will include all participants in the safety population, and the dependent variable will be the observed change from each baseline to Week 12. Covariates in the model will include the fixed categorical effects of treatment, site, sex, current tobacco use status, presence of current MDE, as well as the continuous fixed covariate of baseline score.

The least squares means and 95% confidence intervals (CIs) will be calculated for the treatment difference between the subjects that received TNX-102 SL and placebo in the lead-in study at each time point.

Endpoints reported in this manner will include:

- CAPS-5 Total Score
- Change from baseline in SDS total.
- Change from baseline in participants' quality of sleep using the PROMIS Sleep Disturbance scale.
- Change from baseline in the disruption of work/school activities assessed using the SDS.
- Change from baseline in disruption of social life/ leisure activities assessed using the SDS.
- Change from baseline in the disruption of family life/home responsibilities assessed using the SDS.
- Change from baseline in CAPS-5 Arousal and Reactivity (Criterion E).
- Change from baseline in CAPS-5 Intrusion symptoms (Criterion B).
- Change from baseline in CAPS-5 Negative Cognition and Mood (Criterion D).
- Change from baseline in CAPS-5 Persistent Avoidance (Criterion C).
- Change from baseline in CAPS-5 Sleep Disturbance (item E-6).
- Change from baseline in CAPS-5 Exaggerated Startle (item E-4).
- Change from baseline in CAPS-5 Reckless or Self-Destructive Behavior (item E-2).
- Change from baseline in CAPS-5 Depersonalization (item 29).
- Change from baseline in CAPS-5 Derealization (item 30).

The change from baseline in BDI-II score will be analyzed in a Mixed Model Repeated Measures (MMRM) for the change from each baseline (P301 baseline and P303 baseline)

in separate, independent models. The model will include all participants in the safety population, and the dependent variable will be the observed change from each baseline at each post-randomization visit. Covariates in the model will include the fixed categorical effects of treatment, site, sex, current tobacco use status, presence of current MDE, visit and treatment by visit interaction, as well as the continuous fixed covariates of baseline score and baseline score by visit interaction. An unstructured covariance matrix will be used to model the within-subject variance-covariance errors. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Should the unstructured model fail to converge, an autoregressive AR(1) covariance structure will be attempted, then finally compound symmetric should AR(1) not converge.

The least squares means and 95% confidence intervals (CIs) will be calculated for the treatment difference between the subjects that received TNX-102 SL and placebo in the lead-in study at each time point.

CGI-I score (which does not have baseline assessments) will use the same method, however, the observed baseline response and associated interactions removed from the list of covariates. All visits will be included in the analysis. P-values from these comparisons will be considered nominal.

For each outcome, descriptive statistics (mean, SD, median, minimum and maximum) will be reported as well as LS means, standard error (SE) and p-values comparing the arms at each visit. In addition, for the SDS, the frequency of participants not working or attending school due to reasons unrelated to PTSD will be reported overall and within each visit.

9.1.2 Categorical outcomes

Binary data over time will be analyzed using a Cochran Mantel Haenszel (CMH) test stratified by presence of current major depressive episode. Participants with missing data will be analyzed as though they are non-responders. This will be reported for each endpoint. Differences in proportions along with two-sided 95% CIs will also be reported. Two-sided p-values for the test of no difference between the treatment groups will be provided.

These endpoints will include:

- Proportion of participants with a CGI-I score of “much improved” or “very much improved”.
- Proportion of participants with a ≥50% improvement from baseline in Total CAPS-5 score.

10. SAFETY AND TOLERABILITY ANALYSIS

The safety analysis will be run on the Safety population. The analysis of safety assessments in this study will include summaries of the following safety and tolerability data collected for each participant:

- Adverse Events

- Clinical Laboratory Investigations
- C-SSRS
- Vital Signs
- Visual Examinations of Oral Cavity
- BDI-II

Summaries of continuous parameters will include raw values and change from baseline, as appropriate. Listings of safety data will also be presented.

10.1 Adverse Events

All AEs, newly-emergent adverse events (NEAEs), and SAEs will be coded using MedDRA, version 19.0.

Newly emergent adverse events (NEAEs) are defined as any new AE that started after the patient's first dose of P303 study drug, or any unresolved AE first reported in P301 that exhibited an increase in severity, frequency or relationship after the patient's participation in P303 had begun.

An AE summary table will be presented for the following:

- NEAEs by severity
- NEAEs leading to study drug discontinuation
- NEAEs by relationship
- SAEs
- Oral Cavity NEAEs
- All AEs (including both NEAEs and ongoing AEs from the lead-in study)
- All Oral Cavity AEs (including both Oral Cavity NEAEs and ongoing Oral Cavity AEs from the lead-in study

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 NEAEs, NEAEs by maximum severity, NEAEs by strongest relationship to study drug, oral cavity NEAEs, all AEs (including both NEAEs and ongoing AEs from the lead-in study), and all oral cavity AEs (including both oral cavity NEAEs and ongoing oral cavity NEAEs from the lead-in study).

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

Additionally, a summary of the Oral Cavity AE characteristics will be presented; this includes information such as temporal proximity to the dose, duration and whether the AE was present the following morning.

Adverse events of special interest pertaining to abuse potential will be analyzed separately by treatment group, SOC and preferred term, and displayed in tabular format. Terms to be included may be found in Appendix 3.

In the AE data listings, all AEs will be displayed. A separate by-patient listing of oral cavity AEs (including oral cavity AEs that were ongoing from P301) will be provided. AEs that are newly-emergent will be flagged in all AE listings.

10.1.1 Adverse Events Leading to Discontinuation of Study Drug

A summary of incidence rates (frequencies and percentages) of NEAEs leading to discontinuation of study drug by treatment group, SOC, and preferred term will be prepared for the Safety population.

A data listing of AEs leading to discontinuation of study drug will also be provided, displaying details of the event(s) captured on the CRF.

10.1.2 Serious Adverse Events

A summary of incidence rates (frequencies and percentages) of SAEs by treatment group, SOC, and preferred term will be prepared for the Safety population. A data listing of SAEs will also be provided, displaying details of the event(s) captured on the CRF.

10.1.3 Deaths

A listing of deaths will also be provided for the Safety Population.

10.2 Clinical Laboratory Evaluations

Laboratory data include analyses for Chemistry and Hematology and will be summarized by treatment and visit for the Safety Population. Descriptive summaries of actual values and changes from each baseline will be presented by study visit and each treatment group. 95% confidence intervals will be presented for change from each baseline for each visit. ET data will be analyzed with the closest visit that does not have a valid assessment value.

Laboratory values will be displayed in the data listings and those that are outside the normal range (“H” or “L”) will be flagged, along with corresponding normal ranges. Values pre-defined as potentially clinically significant (“HH” or “LL”) will also be flagged. For each laboratory analysis, shifts in assessments of abnormality from each baseline to each scheduled time point will be presented in shift tables.

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

10.3 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is an instrument that measures suicidal ideation and behavior. Items measuring suicidal ideation and suicidal behavior are displayed in the table below. Frequency counts of yes/no responses to items below and whether any suicidal ideation or behavior is present will be summarized as described below.

The overall number of participants with any suicidal ideation or behavior (by type and in total) or self-injurious behavior while on-treatment will be provided by treatment group. For ideation, participants will only be counted once at each visit and/or time frame at the worst case response for ideation type (1-5), where 1 is the least severe and 5 is the most severe type of ideation.

Category	Items
A) Suicidal Ideation	(1) Type 1: Wish to be dead (2) Type 2: Non-specific active suicidal thoughts (3) Type 3: Active suicidal ideation with any methods (not plan) without intent to act (4) Type 4: Active suicidal ideation with any some intent to act, without specific plan (5) Type 5: Active suicidal ideation with specific plan and intent
B) Suicidal Behavior	(1) Preparatory acts or behavior (2) Aborted attempt (3) Interrupted attempt (4) Actual attempt (5) Completed suicide Suicidal Behavior present (composite of items 1-5) Non-Suicidal Self-Injurious Behavior

Suicidal intensity of ideation will be calculated by tallying up the five intensity items to create a total score ranging 0-25. If a participant does not have any suicidal ideation, a score of 0 will be given. Separate tables will be created for the entire Safety Population as well as the population comprising only participants exhibiting any suicidal ideation. Suicidal intensity of ideation total score will be summarized using descriptive statistics by treatment group.

A data listing of C-SSRS results will include only participants with suicidal ideation, suicidal behavior, or self-injurious behavior without suicidal intent. For participants with suicidal ideation, suicidal behavior, or self-injurious behavior without suicidal intent at any time, data from all visits are displayed.

10.4 Vital Signs

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

These summaries will be presented by treatment and assessment time for the Safety population. ET data will be analyzed with the closest visit that does not have a valid assessment value.

10.5 Visual Examination of Oral Cavity

A visual examination of the oral cavity will be assessed at Baseline and Week 12. A visual examination is to be done any time a participant spontaneously reports an oral adverse event (aside from AEs known to be sensory-only, such as numbness, tingling or bitter taste) to confirm presence or absence of any signs of irritation or other visible

abnormalities. A data listing of the visual examination results performed at each scheduled visit and at the time of an adverse event will be presented.

11. MEDICATIONS

11.1 Concomitant Medication

All medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) Version September 2016. Prior and concomitant medications will be summarized by treatment group and by the number and percentage of participants taking each medication, classified by using WHO-DD Anatomical Therapeutic Chemical Level 3 and preferred term.

Prior medications are defined as medications or therapies initiated prior to the start of the study drug and terminating prior to the start of study drug in protocol P301. 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 participant receives concurrently with the study drug. These medications will have end dates on or after the first dose date of the study drug until ten days after last dose date.

There should be no new prior medications recorded in protocol P303 as these should be captured entirely in P301. Concomitant medications will be summarized by treatment group. All medications will be presented in a listing.

Please refer to Section 7.3 for the conventions used to impute partial start dates and end dates of concomitant medications.

11.2 Exposure and Compliance

The treatment duration will be calculated as (number of days=last dose date - first dose date+1) and summarized. Participants that are lost to follow up or have a missing last dose date will be assigned a last dose date of the day before the last attended clinic visit for analysis purposes.

All pill count shortage (negative pill count) of greater than 4 doses (8 tablets) per 4-week assessment period and/or any between-visit compliance <70% will be considered protocol deviations, and the reason for the pill count discrepancy will be discussed with the participant and documented in the CRF to ensure that any cases of potential abuse or misuse are identified. Participants with more than one significant incidence of negative pill count discrepancy during the double-blind phase of the study will be closely monitored by the investigator.

Exposure will be measured using the last date of treatment and first date of treatment. Total exposure will be defined as the last date of treatment minus the first date of treatment plus one. The number of participants with total exposure by visit weeks ($\leq$ 4 weeks (study day 0 to 28), 4 to $\leq$ 8 (study day 29 to 56), 8 to $\leq$ 12 (study day 57 to 84) and > 12 weeks (study day $\geq$ 85)) will be presented. Additionally, exposure days, defined as the total number of tablets taken divided by 2 (and rounded up to the nearest whole number), will be summarized.

Compliance will similarly be summarized across all study visits for each treatment arm. Study drug compliance as a percentage will be defined as the number of pills taken by the participant divided by the total number of pills that the participant was assigned to take multiplied by 100.

For calculating the compliance and exposure days, the following convention will be applied: for periods where drug is issued, but the participant does not return any bottles or tablets, or the participant misses the visit entirely, that period will not contribute to the compliance or exposure calculation unless the bottles are returned at a later visit.

Compliance will be summarized with descriptive statistics by treatment arm. The number and percentages of participants within certain categories of compliance e.g. < 50%, 50% to < 70%, 70% to <= 100%, greater than 100% will be presented. Compliance between 70% to 114% will not be considered a protocol deviation. Tablet counts, calculation of compliance overall and by visit, and participant-reported reasons for all tablet discrepancies at all visits will be presented in a listing.

In addition, participants with significant over-usage or otherwise unaccounted-for missing tablets resulting in >114% compliance for any visit (e.g., failure to return >8 tablets per 4 week interval) will be summarized by visit and overall. These listings will include both the participant-reported reason for the discrepancy plus the investigator's assessment of potential abuse, misuse or diversion. Tables will be created for higher level abuse-related MedDRA terms. Clinically significant drug accountability discrepancies associated with missing medication, loss of drug, or cases in which the PI confirms concern over drug abuse, misuse or diversion, will be examined and discussed in the CSR.

12. CHANGES FROM PLANNED ANALYSIS

Study day as it appears in data listings and the Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets will differ from the protocol: The protocol describes the day of first dose as "Day 0"; the listings and datasets will conform to the standard of first dose day appearing as "Day 1".

13. REFERENCES

Guidance for Industry Adaptive Design Clinical Trials for Drugs and Biologics, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), February 2010.

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Davidson J, Rothbaum BO, Tucker P, Asnis G, Benattia I, Musgnung JJ. Venlafaxine extended release in posttraumatic stress disorder: a sertraline- and placebo-controlled study. J Clin Psychopharmacol. 2006;26(3):259-67.

Krystal JH, Rosenheck RA, Cramer JA, Vessicchio JC, Jones KM, Vertrees JE, Horney RA, Huang GD, Stock C; Veterans Affairs Cooperative Study No. 504 Group. Adjunctive risperidone treatment for antidepressant-resistant symptoms of chronic military service-related PTSD: a randomized trial. JAMA. 2011;306(5):493-502.

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Weathers FW, Blake DD, Schnurr PP, Kaloupek DG, Marx, et al. The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). 2013: Instrument available from the National Center for PTSD at www.ptsd.va.gov.

14. APPENDICES

14.1 Appendix 1

The following reporting conventions will be adopted for the presentation of study data. These conventions will enhance the review process and help to standardize presentation with common notations.

14.1.1 General Reporting Conventions

- All tables and data listings will be developed in Landscape Orientation, unless presented as part of the text in a clinical study report (CSR).
- Figures will be presented in Landscape Orientation, unless presented as part of the text in a CSR.
- Legends will be used for all figures with more than one variable or item displayed.
- Figures will be in black and white, unless color figures have been identified as useful for discriminating presentation in the figure. Lines in figures should be wide enough to view the line after being photocopied.
- Specialized text styles, such as bolding, italics, borders, shading, superscripted and subscripted text will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard characters should be used in tables and data listings. Special characters, such as non-printable control characters, printer specific, or font specific characters, will not be used on a table, figure, or data listing. Hexadecimal character representations are allowed (e.g., μ, α, β).
- All titles will be centered on a page. The ICH numbering convention is to be used for all tables, listings, and graphs (TLGs).
- All footnotes will be left justified at the bottom of a page. Footnotes must be present on the page where they are first referenced. Footnotes should be used sparingly and must add value to the TLG. If more than four footnote lines are planned then a cover page may be used to display footnotes.
- Missing values for both numeric and character variables will be presented as blanks in a table or data listing. A zero (0) may be used if appropriate to identify when the frequency of a variable is not observed.
- All date values will be presented as YYYY-MM-DD (e.g., 2001-10-17) format. A four-digit year is preferred for all dates.
- All observed time values will be presented using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds should only be reported if they were measured as part of the study.
- Time durations will be reported in mixed HHhr MMm SSs notation (e.g., 5h 32m, or 27h 52m 31s). The use of decimal notation to present (display) time

durations should be avoided (e.g. 0.083h = 5m) unless it is necessary to show the computation of time differences in a table, figure, or data listing, in which case both notations may be used to display the time duration.

- All TLGs will have the name of the program, location, programmer, and a date stamp on the bottom of each output.
- All analysis programs developed for a TLG display will be self-contained to facilitate transfer of programs to multiple computing environments and transfer to a regulatory agency (if requested).

14.1.2 Population Summary Conventions

- Population(s) represented on the tables or data listings will be clearly identified in the last title of the Table as "<name of population>" and will be identical in name to that identified in the protocol or SAP.
- Consistent terminology will be used to define and identify a population. Common nomenclature may include (a) All Participants, (b) ITT, (c) Safety, and (d) PP.
- Sub-population(s) or special population(s) descriptions will provide sufficient detail to ensure comprehension of the population (e.g., MITT >60 years of age) used for analysis in a table or figure.
- Population sizes may be presented for each treatment or dosing category as totals in the column header as (N=xxxx), where appropriate.
- Population sizes shown with summary statistics are the samples sizes (n) of Participants with non-missing values.
- All population summaries for categorical variables will include all categories that were planned and for which the Participants may have had a response. Percentages corresponding to null categories (cells) will be suppressed.
- All population summaries for continuous variables will include: n, mean, SD, minimum, and maximum. Other summaries (e.g. number missing, median, quartiles, 95% confidence intervals, CV or %CV) may be used as appropriate.
- All percentages are rounded and reported to a single decimal point (xx.x%). A percentage of 100% will be reported as 100%. A percentage of zero will be reported as 0.
- Population summaries that include *P* values will report the *P* value to three decimal places with a leading zero (0.001). All *P* values reported on default output from statistical software (i.e., SAS® Software) may be reported at the default level of precision. *P* values <0.001 should be reported as <0.001 not 0.000.

14.2 Appendix 2: PROMIS T-score Conversions

Adult v1.0 - Sleep Disturbance 8a Short Form Conversion Table		
Raw Score	T-score	SE*
8	30.5	4.9
9	35.3	3.7
10	38.1	3.3
11	40.4	3.1
12	42.2	3
13	43.9	2.9
14	45.3	2.8
15	46.7	2.7
16	47.9	2.7
17	49.1	2.6
18	50.2	2.6
19	51.3	2.6
20	52.4	2.6
21	53.4	2.6
22	54.3	2.5
23	55.3	2.5
24	56.2	2.5
25	57.2	2.5
26	58.1	2.5
27	59.1	2.5
28	60	2.5
29	61	2.5
30	62	2.6
31	63	2.6
32	64	2.6
33	65.1	2.6
34	66.2	2.7
35	67.4	2.8
36	68.7	2.9
37	70.2	3
38	72	3.2
39	74.1	3.5
40	77.5	4.2
*Standard Error on T-score metric		

14.3 Appendix 3: Abuse Terms

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

Category	MedDRA Preferred Term
Central nervous system depression terms	Bradyphrenia
	Depression
	Dysphoria
	Hypersomnia
	Hypersomnia related to another mental condition
	Infant sedation
	Neonatal oversedation
	Post-injection delirium sedation syndrome
	Sedation*
	Sedation complication
	Sedative therapy
	Somnolence*
	Somnolence neonatal
	Stupor
Central nervous system stimulation terms	Affect lability
	Aggression
	Agitation
	Anxiety
	Disinhibition
	Energy increased
	Feeling jittery
	Flight of ideas
	Hypervigilance
	Irritability
	Psychomotor hyperactivity
	Restlessness
Dissociative/psychotic-related terms	Abnormal behaviour
	Acute psychosis
	Amnesia
	Delirium
	Delusion
	Delusion of grandeur

	Delusional perception
	Depersonalisation
	Depersonalisation/derealisation disorder
	Derealisation
	Disturbance in attention
	Hallucination
	Hallucination, auditory
	Hallucination, gustatory
	Hallucination, olfactory
	Hallucination, synaesthetic
	Hallucination, tactile
	Hallucination, visual
	Hallucinations, mixed
	Hypnagogic hallucination
	Hypnopompic hallucination
	Mixed delusion
	Psychotic disorder
	Sensory disturbance
	Substance-induced psychotic disorder
	Thinking abnormal
	Transient psychosis
Euphoria-related terms	Elevated mood
	Euphoric mood
	Feeling drunk
	Feeling of relaxation
General terms	Dependence
	Drug abuse
	Drug abuser
	Drug dependence
	Drug dependence, antepartum
	Drug dependence, postpartum
	Drug diversion
	Drug use disorder
	Drug use disorder, antepartum
	Drug use disorder, postpartum

	Drug withdrawal convulsions
	Drug withdrawal headache
	Drug withdrawal maintenance therapy
	Drug withdrawal syndrome
	Drug withdrawal syndrome neonatal
	Substance abuse
	Substance abuser
	Substance dependence
	Substance use disorder
	Withdrawal arrhythmia
	Withdrawal catatonia
	Withdrawal hypertension
	Withdrawal syndrome
Terms not captured elsewhere	Confusional state
	Disorientation
	Emotional disorder
	Feeling abnormal
	Homicidal ideation
	Inappropriate affect
	Intentional misuse of drug delivery system
	Intentional product misuse
	Logorrhoea
	Mania
	Memory impairment
	Mental disorder
	Mood altered
	Mood disorder due to a general medical condition
	Mood swings
	Overdose
	Prescription form tampering
	Product tampering
	Substance-induced mood disorder
	Suicidal ideation
	Suspected product tampering

*Anticipated drug effects